



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 16

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 16

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Advances in
HETEROCYCLIC
CHEMISTRY

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Preface

In this volume three of the chapters deal with specific ring systems: 1,2,3-triazoles (T. L. Gilchrist and G. E. Gymer), dibenzothiophenes (J. Ashby and C. C. Cook), and the 7-azabicyclo[2.2.1]heptadienes, and their reduced, and benzo-fused, derivatives (L. J. Kricka and J. M. Vernon). Three further chapters cover particular aspects of heterocyclic compounds in general: cationic cycloaddition reactions (C. K. Bradsher), homolytic aromatic substitution (F. Minisci and O. Porta), and base-catalyzed hydrogen exchange (of ring protons) (J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard).

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Base-Catalyzed Hydrogen Exchange

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I. Introduction

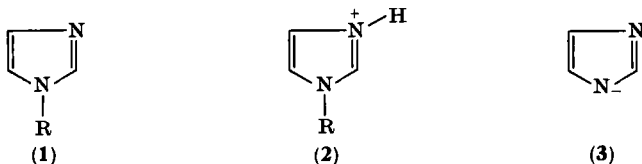
Proton-transfer reactions continue to be of extensive interest¹ and the subject of much discussion² but, while a great deal of attention has been given to carbon acids such as ketones and nitro compounds, work on heterocyclic compounds has been less extensive. There are, however, good grounds for believing that studies in this area could be rewarding and should therefore be encouraged. A knowledge of the effect of position and type of heteroatom on the rates of proton transfer raises the possibility of being able to dissect quantitatively the contributions from inductive, coulombic, resonance, *d*-orbital, and *s*-character effects. Such an analysis becomes possible only when the various contributions are independent of one another. A further comparison of rates of exchange with analogous reactions of structurally similar heteroaromatics

¹ R. P. Bell, "The Proton in Chemistry." Methuen, London, 1961.

² *Discuss. Faraday Soc.* **39**, (1966).

could provide information concerning the use of, for example, ylide intermediates.

Many heterocyclic compounds contain ionizable groups other than $>\text{C}-\text{H}$, for example, $>\text{N}-\text{H}$, and in these cases the molecules may undergo reaction in a protonated or a deprotonated form rather than as the neutral molecule. Thus imidazole (**1**, $\text{R} = \text{H}$), may exist in solution as the conjugate acid (**2**) or conjugate base (**3**). Such ionized forms frequently serve as substrates in enzymatic processes and in order to improve



our understanding of the specificity of enzymes and the mechanisms of the reactions involved it seems desirable to look at the ionization reactions of such compounds.

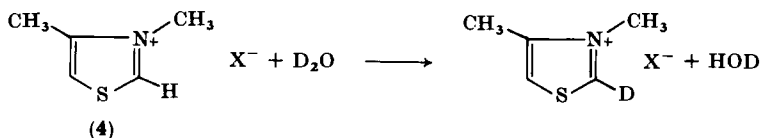
Compounds labeled with deuterium or tritium are becoming increasingly important in reaction mechanism studies of both chemical and biological systems. Sometimes the need to prepare specifically labeled molecules has been presented as a considerable barrier to such investigations. Isotopic hydrogen exchange is, however, becoming a widely employed method for preparing labeled compounds, being unsatisfactory only when the specificity of the process is uncertain and the ease with which the label can be replaced is high. A better understanding of the various factors involved in the preparation of labeled compounds, as well as the stability of the label under widely different conditions, would therefore be welcome. It is for these different reasons that the present review on base-catalyzed exchange has been undertaken. A review on the related metal-catalyzed exchange in heterocyclic compounds has already appeared.^{2a}

II. Experimental Methods

There are three methods that are widely used to follow the rates of isotopic hydrogen exchange in heterocyclic compounds. First, infrared spectroscopy enables the replacement of a hydrogen atom by a deuterium atom within a molecule to be detected. When an $\text{X}-\text{H}$ bond becomes an $\text{X}-\text{D}$ bond there is a reduction in the stretching frequency

^{2a} G. E. Calf and J. L. Garnett, *Advan. Heterocycl. Chem.* **15**, 137 (1973).

by a factor close to $2\frac{1}{2}$. Thus, the development of an intense band at $4.5\ \mu$ in the infrared demonstrates that 3,4-dimethylthiazolium bromide (4, $X = \text{Br}$) undergoes hydrogen-deuterium exchange at C-2 in neutral D_2O at room temperature.³ The observation indicates the replacement of hydrogen by deuterium at a carbon atom which is part of a highly polarizable double bond rather than at a saturated carbon atom. Loss of a band near $11.0\ \mu$ (out of plane C—H bonding) also indicates replacement of the same hydrogen atom. The infrared method thus makes it possible to distinguish between different groups such as



>C—H , —O—H , and >N—H , and this fact enabled Fritzsche⁴ to ascribe the slow hydrogen-deuterium exchange of DNA to replacement at the C-8 hydrogen of the adenine and guanine residues.

Second, nuclear magnetic resonance gives both the position and rate of exchange from a single experiment. This is particularly important for heterocyclic compounds because otherwise misinterpretation is possible, e.g., hydrogen-deuterium exchange⁵ of *N*-methyl-2-pyridone occurs at C-6, although exchange at the methyl group under similar conditions has been claimed.⁶ Similarly, some doubts have been expressed as to the site of exchange in hypoxanthines.

It is customary practice to follow changes in spectra as a function of time. The integral amplitude corresponding to the reaction site is normalized by reference to a nonexchanging internal standard. Rates of dedeuteration as well as deuteration can be measured. The main features of the method are that it provides a continuous measurement of the extent of exchange so that no chemical separations are necessary, requires relatively concentrated solutions of substrate (0.1–0.5 M), is currently of relatively low accuracy (± 10 –20% is frequently quoted), and requires solvents with spectra which do not overlap with resonances of exchanging group(s) of the compound in question. Recent developments include the use of digital computers to improve signal-to-noise ratio and provide detailed spectral analysis; in principle, rates of detritiation (or tritiation) can be followed as tritium is an excellent isotope for

³ R. Breslow, *J. Amer. Chem. Soc.* **80**, 3719 (1958).

⁴ H. Fritzsche, *Biochim. Biophys. Acta* **149**, 173 (1967).

⁵ P. Beak, J. Bonham, and J. T. Lee, *J. Amer. Chem. Soc.* **90**, 1569 (1968).

⁶ B. S. Thyagarajan and K. Rajagopalan, *Tetrahedron* **19**, 1483 (1963).

nuclear magnetic resonance studies⁷ with a sensitivity to detection which is 20% higher than that of the proton. Even so, a relatively high concentration ($> 0.01\%$ isotopic abundance) is necessary for NMR detection, and at present this limits the reactions that can be studied to those in which radiation-induced exchange is unimportant.

An example of the application of the NMR method³ is provided by a study of 3,4-dimethylthiazolium iodide (4, $X = I$) in D_2O solution. The spectrum initially contains four peaks, two of equal intensity at low field due to protons at C-2 and C-5, and two others of triple the magnitude at higher field, assigned to the protons of the methyl groups. The peak at lowest field must be due to the proton at C-2, which should have the greatest chemical shift due to the proximity of the positive nitrogen, and this is the peak which disappears on standing in D_2O , the half-life being of the order of 20 minutes.

Finally, radiochemical methods of analysis may be used to follow rates of detritiation. This method is particularly useful for very slow reactions (where it is impractical to collect data for any appreciable extent of reaction) as an initial rate approach may then be employed. Separation difficulties, at least for aqueous solutions, may be overcome by using the freeze-drying method or the more recent countercurrent dialysis and Sephadex gel filtration techniques.⁸

III. Five-Membered Rings

A. CONTAINING TWO NITROGEN ATOMS

Conflicting reports of exchange reactions of imidazole have been published. Gillespie *et al.*⁹ described the exchange at the 2-position as being base-catalyzed and involving the conjugate base of imidazole (3). Others have observed the reaction in the absence of base and found that 1-benzylimidazole (1, $R = C_6H_5CH_2$), which cannot form the conjugate base, undergoes quite fast exchange at the 2-position.¹⁰ Harris and Randall¹¹ followed the dedeuteration of $[2,4,5-^2H_3]$ -1-methylimidazole

⁷ J. Bloxsidge, J. A. Elvidge, J. R. Jones, and E. A. Evans, *Org. Magn. Resonance* **3**, 127 (1971).

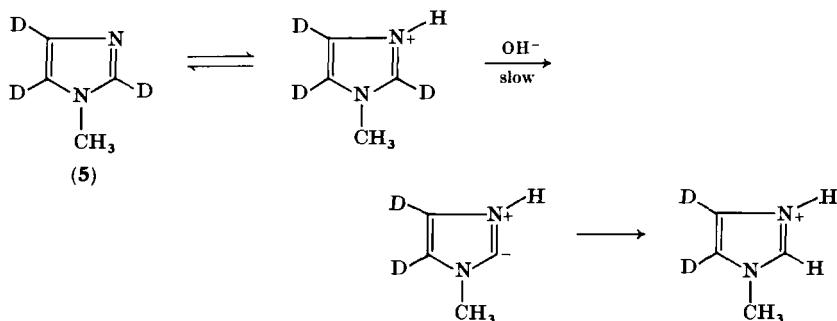
⁸ S. W. Englander, "Poly- α -Amino Acids," p. 339. Dekker, New York, 1967.

⁹ R. J. Gillespie, A. Grimison, J. H. Ridd, and R. F. White, *J. Chem. Soc.*, 3228 (1958).

¹⁰ H. A. Staab, M.-Th. Wu, A. Mannschreck, and G. Schwalbach, *Tetrahedron Lett.* 845 (1964).

¹¹ T. M. Harris and J. C. Randall, *Chem. Ind. (London)*, 1728 (1965).

(5) in solutions of varying pH and found the rate to be essentially unaffected in the alkaline region but rapidly reduced to zero in acidic solutions. This result was consistent with a mechanism in which the conjugate acid of 1-methylimidazole is attacked by hydroxide ions to form an ylide in the rate-determining step (Scheme 1):



Haake *et al.*¹² reported on the H/D exchange from the 2-position of 1,3,4-trimethylimidazolium ion (6) and found the predominant exchange pathway to involve OD^- as base. The rate is approximately 3×10^3 times slower than that at which the deuteroxide ion abstracts a proton from structurally similar thiazolium ions, in contrast with previous work¹³ where a diphenylimidazolium ion was found to exchange at the



same rate as a thiazolium ion. The fact that the azolium ions differed considerably in structure might be the reason. Olofson, Thompson, and Michelman¹⁴ found exchange from the 2-position of 1,3-dimethylimidazolium ion at 31° to be catalyzed by OH^- , thus showing the greatly enhanced reactivity of the imidazolium ion over the neutral species. The rate was also 3×10^4 times faster than that of the pyrazolium salt

¹² P. Haake, L. P. Bauscher, and W. B. Miller, *J. Amer. Chem. Soc.* **91**, 1113 (1969).

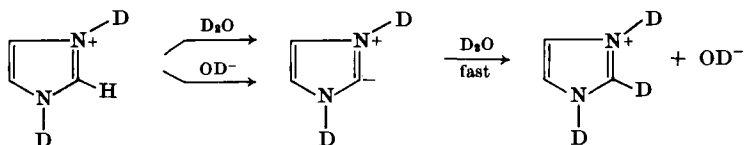
¹³ W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry* **2**, 1298 (1963); **3**, 1072 (1964).

¹⁴ R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.* **86**, 1865 (1964).

(7), where only one of the two positively charged nitrogens is α to the forming carbanion.

Rates of deuteration of imidazole have been measured at various pD values at 65° and 70° for the 2-position, and at 180° and 190° for the 4(5)-positions.¹⁵ The difference in reactivity can be ascribed to the fact that the 2-H has the advantage of the inductive effect of one α -nitrogen and one positively charged α -nitrogen, whereas the 4(5)-position has a β -nitrogen and one positively charged α -nitrogen. Small differences in bond angles at C-2 and C-4 may also reflect a difference in s -character and hence acidity.

The rate-pD profile for the 2-position could be accounted for by parallel rate-determining proton abstraction from the conjugate acid of imidazole by OD^- and by D_2O leading to an ylide intermediate (Scheme 2). These pathways together with OD^- -catalyzed proton abstraction from the neutral imidazole molecule accounted for the 4(5)-



SCHEME 2

position profiles. The 2-position profile is in fact similar to that observed for 1-methylimidazole¹¹ except that a nonvanishing rate of deuteration was observed for imidazole even at high acidities.

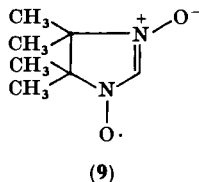
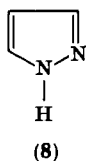
Although the data do not rule out other mechanistic pathways for 4(5)-deuteration, e.g., the conjugate base of imidazole could react with D_2O to form a σ -intermediate followed by proton removal to yield the products, this seems unlikely by analogy with the results¹⁶ obtained for the corresponding 1,2-isomer, pyrazole, where the rate of deuteration of 3(5)-positions does not exhibit buffer catalysis or pD dependence. For hydrogen exchange at the 3(5)-positions of pyrazole (8) the possibility of a rate-determining attack by D_3O^+ on the conjugate base was ruled out by Olofson's finding that the deuteration of 1,2-dimethylpyrazolium iodide (7) was catalyzed by deuteroxide ions. Exchange at the 4-position of pyrazole was consistent with general acid catalyzed attack on the neutral and protonated forms.

The ready exchange (at 23° in D_2O) of the 2-H of the nitronyl nitroxide

¹⁵ J. D. Vaughan, Z. Mughrabi, and E. Chung Wu, *J. Org. Chem.* **35**, 1141 (1970).

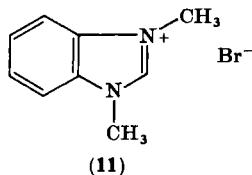
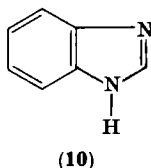
¹⁶ E. Chung Wu and J. D. Vaughan, *J. Org. Chem.* **35**, 1146 (1970).

radical¹⁷ (9) is reminiscent of heterocyclic cations. The exchange data suggest two independent mechanisms: one is solvent-catalyzed and operative at low pD, the other involves hydroxide-catalyzed abstraction of the 2-H to give the radical anion and is dominant above pD 7. The exceptional acidity of 9 is possibly due to the effect of two nitrogens adjacent to the acidic site which are estimated from the nitrogen-coupling constants to bear a total positive charge of nearly 1.6.



Fritzsche⁴ observed that in D₂O benzimidazole exchanged its 2-H on prolonged heating. The rates of exchange of both this compound and the 1-methyl analog have been measured in C₂H₅OD at various temperatures from 35° to 80°, the latter being slightly the faster.¹⁸ The rate of exchange of the 2-H for the 1-methyl compound was also faster in a medium of 0.6 N C₂H₅OK in C₂H₅OD than in C₂H₅OD alone, suggesting that in this highly basic medium some reaction occurs between the ethoxide ion and the neutral benzimidazole molecule. 1-Benzylimidazole also undergoes exchange¹⁰ at the 2-position in MeOD at 60°.

Rates of detritiation of [2-³H]-benzimidazole (10) and the corresponding 1-methyl compound have been measured over a pH range at 85° and the bell-shaped pH-rate profile (Fig. 1) accounted for in terms of rate-determining attack by OH⁻ on the benzimidazole cation with the formation of an ylide intermediate.¹⁹ Because of the ionization of the N-H group at high pH, the development of negative charge α to the



¹⁷ D. G. B. Boocock, R. Darcy, and E. F. Ullman, *J. Amer. Chem. Soc.* **90**, 5945 (1968).

¹⁸ N. N. Zatsepina, Yu. L. Kaminski, and I. F. Tupitsyn, *Reakts. Sposobnost Org. Soedin.* **4**, 433 (1967), *Org. React. (USSR)* **4**, 177 (1967).

¹⁹ J. A. Elvidge, E. A. Evans, J. R. Jones, C. O'Brien, and J. C. Turner, *J. Chem. Soc., Perkin Trans. II*, 432 (1973).

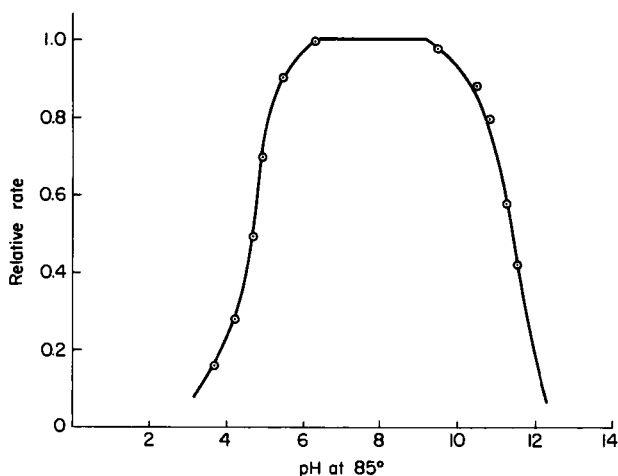
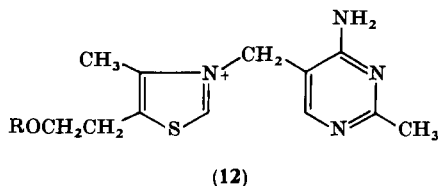


FIG. 1. Rate vs. pH profile for $[2\text{-}^3\text{H}]$ -benzimidazole; — represents calculated curve.

position undergoing reaction makes the anion unreactive to exchange; for imidazole the anion is formed only in still more basic media and its pH-rate profile resembles that of 1-methylbenzimidazole. The kinetically equivalent possibility of a rate-determining attack by H_2O on the neutral benzimidazole molecule was ruled out by the observation that the second-order rate constant for attack of OH^- on $[2\text{-}^3\text{H}]$ -1,3-dimethylbenzimidazolium bromide (11) was closely similar to that for attack of OH^- on the benzimidazolium cation. The rates of detritiation of several chloro-substituted and 1-alkyl-substituted benzimidazoles (benzyl \sim i-propyl $>$ ethyl $>$ methyl $>$ hydrogen) were consistent with the proposed mechanism.

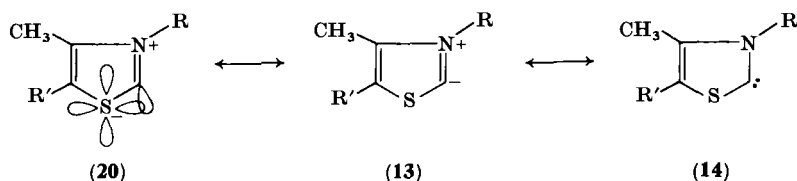
B. CONTAINING ONE NITROGEN AND ONE SULFUR ATOM

Hydrogen exchange of thiazole and thiazolium ions has received much attention since Breslow's observation^{3, 20} that thiamine (12), which in the form of its pyrophosphate, cocarboxylase, is the coenzyme for a

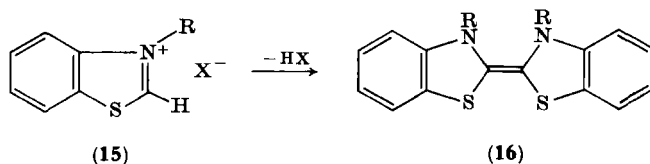


²⁰ R. Breslow, *J. Amer. Chem. Soc.* **79**, 1762 (1957).

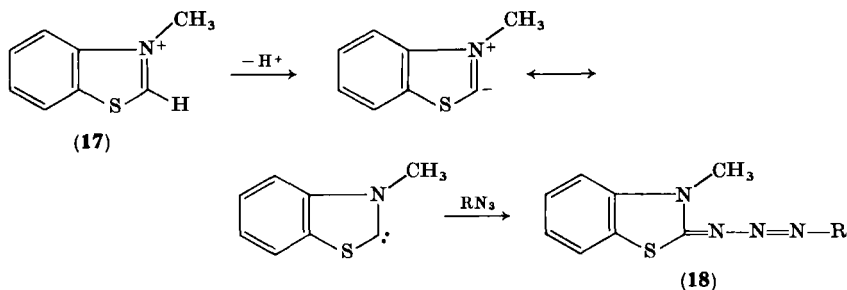
number of biochemical reactions, exchanges its 2-H with a reaction half-life of 20 minutes in D_2O at 28° . This can be compared with the conditions necessary to induce exchange via other nitrogen ylides—imidazole¹⁵ exchanges its 2-H with a reaction half-life of 100 minutes in D_2O at 65° . In contrast tetramethylammonium iodide requires over 10 days of refluxing in 0.27 *M* base to exchange 0.1% of each hydrogen. The remarkable lability of the 2-H in the thiazolium ring has been ascribed to the combined effect of a number of factors. In addition to the high *s*-character of the C-H bond and the operation of inductive effects, the aromatic system has a great potential for enhancing resonance stability, e.g., the ylide (13) can be stabilized by contribution from the carbenelike structure (14).



The existence of carbene intermediates was proposed by Wanzlich,²¹ who found that deprotonation of 1-alkylbenzothiazolium salts (15) led to dimer formation. Quast and Hünig²² also produced a dimer (16,



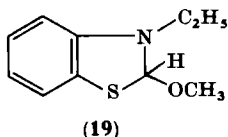
$R = CH_3$) by deprotonation of 1-methylbenzothiazolium salts (17) and were able to trap the carbene by reaction with azides to give isolable triazacyanines (18). In other examples tetracyanoethylene has been



²¹ H. W. Wanzlich, *Angew. Chem. Int. Ed. Engl.* **1**, 75 (1962).

²² H. Quast and S. Hünig, *Angew. Chem. Int. Ed. Engl.* **3**, 800 (1964).

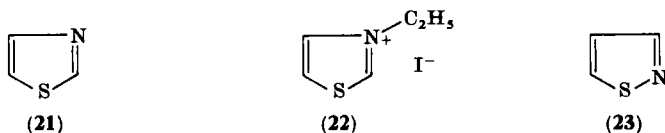
used as a trapping agent.²³ The dimer (**16**, R = C₂H₅), could also be produced by loss of methanol from **19**. It therefore seems probable that the carbene resonance form is a likely contributor to the resonance



stabilization of the thiazolium ylide.

The stability of the ylide (**13**) formed by deprotonation may also owe something to the interaction of a *d*-orbital at sulfur with the σ -orbital directed away from the ring at C-2, leading to **20**. Much recent work has been concerned with obtaining quantitative estimates of the magnitude of these contributions.

Deuteration of the parent compound thiazole (**21**) leading to exchange



at the C-2 hydrogen was first studied by Staab *et al.*¹⁰ using MeOD at 60°. The pH-rate profile²⁴ for exchange at this position suggests that the mechanism involves an equilibrium protonation on nitrogen followed by a rate-determining proton abstraction from C-2 (Scheme 3), but that at high pH a base-induced proton abstraction from the neutral compound becomes predominant (Scheme 4). Confirmation that at lower pH the protonated form is indeed the active intermediate comes from the finding that the rate of exchange is close to that obtained for 3-ethylthiazolium iodide (**22**) under similar conditions.²⁵ The observations that a lithium salt at the 2-position of benzimidazole can be prepared²⁶ and that thiazole-2-carboxylic acid readily decarboxylates,²⁷ presumably through a carbanion intermediate, supports the above mechanism. An alternative, whereby OD⁻ adds on to the C-2 position of thiazole in a rate-determining step, seems much less likely. Exchange at the 5-position was observed only at very high pD, the

²³ H. Balli, *Angew. Chem. Int. Ed. Engl.* **3**, 809 (1964).

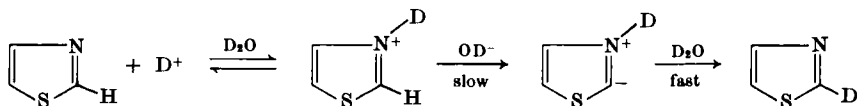
²⁴ R. H. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron* **26**, 685 (1970).

²⁵ R. A. Olofson and J. M. Landesberg, *J. Amer. Chem. Soc.* **88**, 4263 (1966).

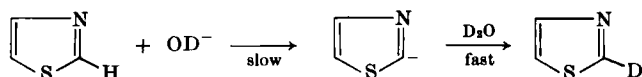
²⁶ F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.* **8**, 257 (1971).

²⁷ H. Schenkel and M. Schenkel, *Helv. Chim. Acta* **31**, 924 (1948).

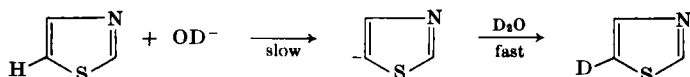
pD-rate profile being consistent with rate-determining attack by OD^- on the 5-H of the neutral thiazole molecule (Scheme 5). Deprotonation of the 2-H and 5-H of the neutral species takes place at approximately the same rate, but considerably slower than that of 5-H in isothiazole (23).²⁸



SCHEME 3



SCHEME 4



SCHEME 5

Superficially it seems to make little difference whether the ring nitrogen is α or β to the carbon bearing the exchanging proton. However, inductive and electronegativity effects must be important, as electron-withdrawing substituents increase the isothiazole rate whereas electron-releasing substituents slow it down.²⁸ It is also clear that coulombic and inductive effects are major rate-enhancing factors, from a study of the rates of deuterium incorporation into a number of positively charged polynitrogen heterocyclic salts.¹⁴ Another effect such as $d-\sigma$ overlap must therefore be operating and this would be consistent with the fact that the exchange rate of protons next to sulfur is invariably greater than the exchange rate of protons on carbon next to nitrogen, in contrast to what one would expect on the basis of reduced electronegativity. Evidence based on quantitative comparison of oxazolium and thiazolium ions gives further support to the suggestion of $d-\sigma$ overlap as a possible stabilizing factor in thiazolium ylides.²⁹

Benzothiazole (24) exchanges¹⁰ its 2-H in MeOD at 60° (at a rate that is three times slower than for thiazole) but³⁰ in MeO^--MeOD at 28° .

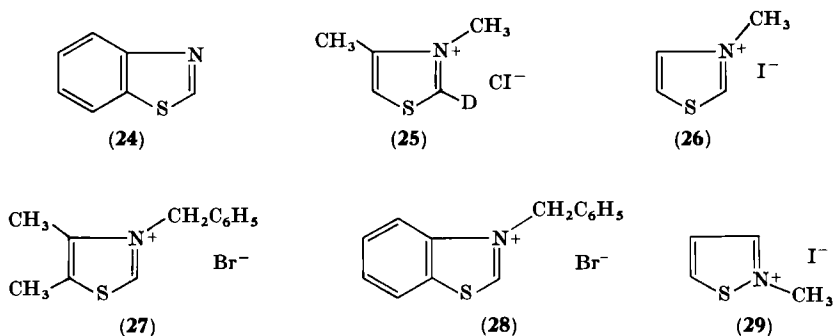
²⁸ R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.* **88**, 4265 (1966).

²⁹ P. Haake and W. B. Miller, *J. Amer. Chem. Soc.* **85**, 4044 (1963).

³⁰ M. Foa, F. Taddei, and P. E. Todesco, *Bull. Sci. Fac. Chim. Ind. Bologna* **23**, 225 (1965).

In $\text{C}_2\text{H}_5\text{OD}$ and in $0.6\text{ }M\text{ C}_2\text{H}_5\text{O}^- - \text{C}_2\text{H}_5\text{OD}$ exchange was still confined to the 2-position but it was appreciably faster in the more basic medium;¹⁸ probably attack of ethoxide ion on both the benzothiazolium cation and neutral molecule is involved.

Rates of dedeuteration of $[2\text{-}^2\text{H}]\text{-3,4-dimethylthiazolium chloride}$ (25) in ethanolic acetate buffers at 25° showed that the reaction was catalyzed by ethoxide ion with no detectable acetate catalysis.³¹ The rate was approximately 500 times faster than for the corresponding bromide in aqueous phthalate buffers, assuming that only hydroxide ions catalyze the exchange in the medium. This, however, may not be strictly correct, as Haake *et al.*³² have detected catalysis by DPO_4^{2-} for this compound with a Brönsted β coefficient of around 0.7. The rate is approximately five times slower than for the 3-methylthiazolium iodide³³ (26). For the latter compound a primary hydrogen isotope effect $k_{\text{H}}/k_{\text{T}}$ of close to 5 was obtained at 28° , a value that can be compared with 2.7 and 4.8 for 3-benzyl-4,5-dimethylthiazolium bromide (27) and 3-benzylbenzthiazolium bromide (28), respectively.³⁴ Overwhelming hydroxide ion catalysis with a Brönsted β coefficient of greater than 0.9 was obtained for the last two compounds.



By comparing rates for the thiazolium cation and neutral thiazole it is clear that the positive charge on the α -nitrogen is worth more than a factor of 10^7 to the exchange rate at the 2-position. Similarly, 2-methylisothiazolium iodide (29) exchanges its 5-H approximately 10^6 times faster than isothiazole itself.²⁵ Substituent effects for isothiazole are similar to those observed for thiazole and the reaction is catalyzed by OD^- with

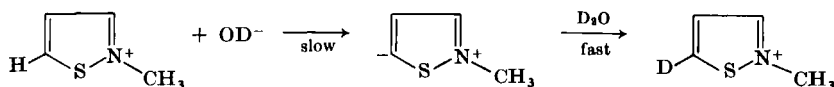
³¹ J. Crosby and G. E. Lienhard, *J. Amer. Chem. Soc.* **92**, 5707 (1970).

³² P. Haake, L. P. Bauscher, and W. B. Miller, *J. Amer. Chem. Soc.* **91**, 1113 (1969).

³³ W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry* **2**, 1298 (1963).

³⁴ D. S. Kemp and J. T. O'Brien, *J. Amer. Chem. Soc.* **92**, 2554 (1970).

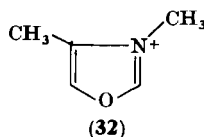
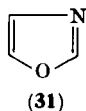
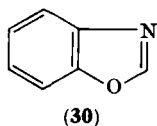
slight buffer base catalysis. The most likely mechanism for exchange involves rate-determining attack by OD^- on the isothiazolium ion leading to a carbanion which then reacts with the solvent in a fast step to give the deuterated product (Scheme 6).



SCHEME 6

C. CONTAINING ONE NITROGEN AND ONE OXYGEN ATOM

Oxazoles exchange their 2-H under both neutral¹⁰ and basic¹⁸ conditions. In MeOD at 60° the rate for benzoxazole (30) was much slower than that for the more basic compound oxazole (31), suggesting that exchange at pH values near 7 takes place by attack of OH^- on the oxazolium cation and not on the neutral oxazole.¹⁰ Benzoxazole also exchanged in $\text{C}_2\text{H}_5\text{O}^-$ - $\text{C}_2\text{H}_5\text{OD}$ much faster than in neutral $\text{C}_2\text{H}_5\text{OD}$, showing that attack by ethoxide ion on the neutral molecule (30) takes place under basic conditions.¹⁸ In the case of the 3,4-dimethyloxazolium ion (32), exchange, having been measured at a variety of pH and buffer concentrations, was found to be catalyzed by OD^- with a small contribution from D_2O or buffer base.³²

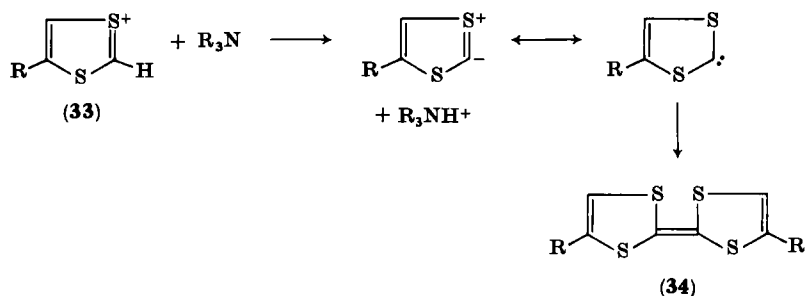


D. CONTAINING TWO SULFUR ATOMS

Unlike their thiazolium, imidazolium, and oxazolium analogs, the dithiolium systems have not been extensively studied. Where measurements have been reported they indicate that hydrogen atoms at positions 2 or 3 possess considerable acidity. The 1,3-dithiolium cation (33, $\text{R} = \text{CH}_3$) exchanged its 2-H in CF_3COOD - D_2O at 34°, OD^- probably being the effective catalyst.³⁵ When 1,3-dithiolium salts dissolved in an

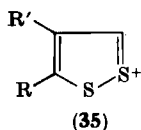
³⁵ H. Prinzbach, H. Berger, and A. Lüttringhaus, *Angew. Chem. Int. Ed. Engl.* **4**, 435 (1965).

aprotic solvent are treated with a tertiary amine, 1,4,5,8-tetrathiofulvalenes (**34**) are formed as mixtures of geometric isomers. This has been interpreted as involving the formation of a carbene intermediate which subsequently dimerizes (Scheme 7).



SCHEME 7

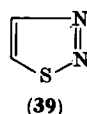
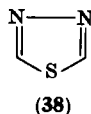
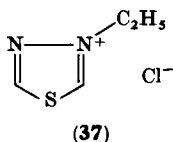
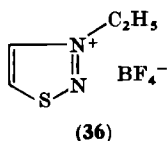
For the 1,2-dithiolium system³⁶ (**35**, $R = C_6H_5$, $R' = H$) exchange was found in the 3-position when carried out in $CF_3COOD-D_2O$ at 74° . The rate decreases as the concentration of acid increases, suggesting base-catalyzed exchange, the mechanism probably being analogous to isothiazolium exchange (Scheme 6).



E. CONTAINING TWO NITROGEN AND ONE SULFUR ATOM

Replacement of a carbon in the thiazolium or isothiazolium cation by nitrogen to yield the thiadiazolium salts (**36**) and (**37**) increases the deprotonation rate by between 10^3 and 10^4 . These compounds as well as 1,3,4-thiadiazole (**38**) and 1,2,3-thiadiazole (**39**) have been studied by Olofson *et al.*^{25, 28} as part of a series of five-membered heterocyclic systems containing nitrogen and sulfur. In all four cases the rate equation is first order in both substrate and OD^- , and the likely mechanism is thought to involve rate-determining proton abstraction by OD^- followed by fast reaction with D_2O to give the exchanged product.

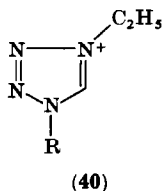
³⁶ H. Prinzbach, E. Futterer, and A. Lüttringhaus, *Angew. Chem. Int. Ed. Engl.* **5**, 513 (1966).



The equivalent 2- and 5-hydrogens of **38** exchanged in OD^- - D_2O at 31° whereas only the 5-H of **39** exchanged under the same conditions. The 2- and 5-H of **37** exchanged with an increase in rate of 10^{10} and 10^6 , respectively, over the neutral 3,4-thiadiazole (**38**), illustrating once again the enormous rate-enhancing effect of having positively charged nitrogen α and β to the exchange site. Similarly, the 5-H of **36** exchanged 10^6 times faster than the 5-H of **39**.

F. CONTAINING FOUR NITROGEN ATOMS

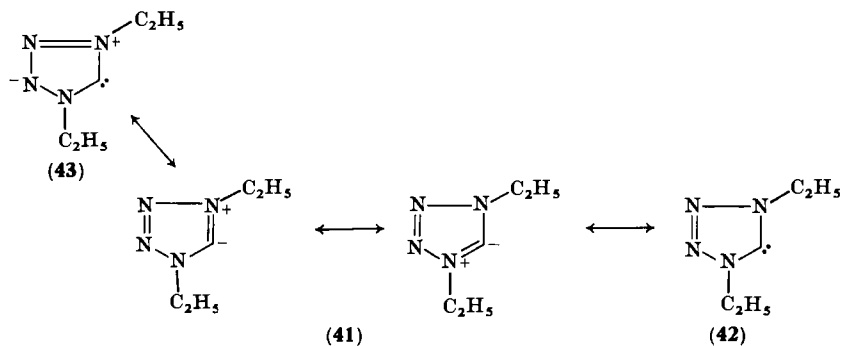
As we have seen, the kinetic acidity of a C-H bond which is sp^2 -hybridized at carbon can be dramatically enhanced by the introduction of adjacent positive charges and electronegative atoms. Consequently the addition of two further nitrogen atoms to the imidazolium ring to form tetrazolium salts should in turn yield very highly stabilized carbanions. 1-Substituted tetrazoles should be among the strongest carbon acids of this type. In fact reaction half-lives for the base-catalyzed deuterium incorporation at C-5 of a series of 1-aryl-4-ethyltetrazolium cations³⁷ (**40**) in 9 *N* $\text{CF}_3\text{CO}_2\text{D}$ are of the order of 1–20 minutes, approxi-



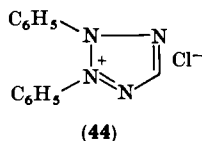
mately 10^9 times as fast as the corresponding imidazolium compounds; the base is thought to be a combination of H_2O and CF_3CO_2^- . The weak base piperidine likewise easily deprotonates the neutral tetrazoles. Attention has been drawn to the possibility that the additional nitrogen atoms exert an effect which is more than purely inductive: They can stabilize the carbene form (**42**) of the zwitterion (**41**) by making new resonance forms possible in which the negative charge can be distributed

³⁷ A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.* 3377 (1969).

over the additional electronegative atoms (43). Thus ionization is facilitated.

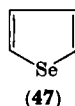
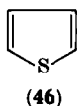
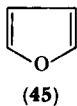


In a separate study¹⁴ the rate of exchange of the 5-H of 2,3-diphenyl-tetrazolium chloride (44) has been found to be approximately the same as that for the 1,3-dimethylimidazolium salt.



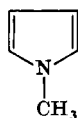
G. CONTAINING ONE HETEROATOM

In contrast to the previous examples, compounds consisting of a five-membered ring with one heteroatom undergo isotopic hydrogen exchange only in highly basic media such as $\text{C}_2\text{H}_5\text{O}^-\text{K}^+$ in $\text{C}_2\text{H}_5\text{OD}$ or $\text{K}^+\text{O}^-\text{Bu-}t$ in CD_3SOCD_3 . Thus Shatenshtein *et al.*³⁸ have found that the relative rates of exchange for the α -deuterium in furan (45), thiophene (46), and selenophene (47) in a 0.4 *M* $\text{KOBu-}t/\text{CH}_3\text{SOCH}_3$ medium are 1:500:700, reflecting the enhanced stabilization of the carbanions through d - σ overlap; presumably selenium is slightly more effective than sulfur in this respect. In all three cases exchange is very much faster than in the 3-position, where the corresponding relative rates are 0.002:0.002:0.015.

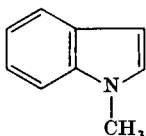


³⁸ A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Yu. I. Ranneva, and E. N. Zvyagintseva, *Dokl. Akad. Nauk SSSR* **168**, 364 (1966).

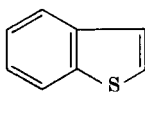
[2- ^2H]-3-Methylthiophene exchanged much more slowly than [2- ^2H]-thiophene, whereas [2- ^2H]-3-methoxythiophene exchanged much faster. The operation of these simple inductive effects were confirmed by the work of Zatsepina *et al.*³⁹ who also investigated the rates of deuteration of *N*-methylpyrrole (48), *N*-methylindole (49), benzothiophene (50), and benzofuran (51) in 0.57 *M* $\text{C}_2\text{H}_5\text{O}^-\text{K}^+$ in $\text{C}_2\text{H}_5\text{OD}$. For exchange in the 2-position the effectiveness of the heteroatom in increasing the rate was $\text{S} > \text{O} > \text{N}$, showing that once more $d\text{-}\sigma$ overlap is operative for sulfur and outweighs the inductive effect of the more electronegative oxygen and nitrogen atoms. The addition of a benzene ring activates exchange at the 2- and 3-positions—for benzofuran exchange at the 2-position is about ten times faster than for furan itself.



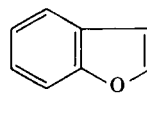
(48)



(49)



(50)



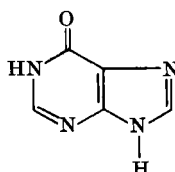
(51)

H. OTHER SYSTEMS

For the biochemically interesting purines formed by fusion of a pyrimidine and imidazole ring, exchange can take place either at the C-2 or C-8 positions. Preliminary results⁴⁰ in the case of adenine (52)



(52)



(53)

show that under neutral conditions the tritium atom at the C-2 position undergoes exchange nearly 2000 times as slowly as from the C-8 position. Previously the ready exchange of the C-8 proton of purines in D_2O at elevated temperatures ($\sim 100^\circ$) had been observed using both NMR⁴¹

³⁹ N. N. Zatsepina, Yu. L. Kaminski, and I. F. Tupitsyn, *Reakts. Sposobnost Org. Soedin.* **6**, 735 (1969); *Org. React. (USSR)* **6**, 320 (1969).

⁴⁰ J. A. Elvidge, J. R. Jones, C. O'Brien, and E. A. Evans, *Chem. Commun.* 394 (1971).

⁴¹ F. J. Bullock and D. Jardetsky, *J. Org. Chem.* **29**, 1988 (1964).

and tritium tracer techniques.⁴² The mechanism of the exchange reaction for several purines has recently been investigated^{43, 44} and turns out to be similar to that observed for imidazole and other related five-membered heterocyclic systems, namely, hydroxide-catalyzed deprotonation at the 8-position in the N-7-protonated compound, with the formation of an ylide intermediate which is then reprotonated in a fast step. Preliminary results⁴⁵ have also been reported for hydrogen-deuterium exchange in hypoxanthine (53). Although details of the mechanism were then obscure, it seems probable that it is the same as for other purines.⁴³

IV. Six-Membered Rings

A. CONTAINING ONE NITROGEN ATOM

The deuteration of benzene requires a highly basic medium before reaction proceeds at an acceptable rate. The insertion of atoms possessing electron-attracting inductive effects such as fluorine, oxygen, or nitrogen into the benzene nucleus should, however, facilitate the formation of carbanions at adjacent centers although examples may be quoted where anion formation is retarded or increased to a much smaller extent than predicted.^{46, 47} For hydrogen-deuterium exchange of pyridine in methanol-methoxide solution⁴⁸ at 165° the reactivity order [2(6) < 3(5) < 4] is the same as that obtained⁴⁹ in D₂O-OD⁻ at 200°, and ND₃-NaN₂⁵⁰ at -25°. Zoltewicz *et al.*⁴⁸ have ascribed the decreased reactivity of the positions adjacent to nitrogen to two reinforcing factors. (1) Geometrical changes, consequent upon the insertion of the heteroatom, lead to a decreased *s*-character of the carbon-hydrogen bond. In pyridine itself the endo angle at C-2 is 4° larger, and at C-3 and C-4, 1° 24' and 1° 54' smaller, respectively, than the 120° angle found in benzene. The angle change at C-2 suggests a 5% reduction in the *s*-character of the C(2)-H

⁴² K. R. Shelton and J. M. Clark, *Biochemistry* **6**, 2735 (1967).

⁴³ C. O'Brien, Ph.D. Thesis, University of Surrey, 1972.

⁴⁴ M. Tomasz, J. Olson, and C. M. Mercado, *Biochemistry* **11**, 1235 (1972).

⁴⁵ F. Bergmann, D. Lichtenberg, and Z. Neiman, *Chem. Commun.* 992 (1969).

⁴⁶ J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.* **89**, 5911 (1967).

⁴⁷ A. Streitwieser and F. Mares, *J. Amer. Chem. Soc.* **90**, 2444 (1968).

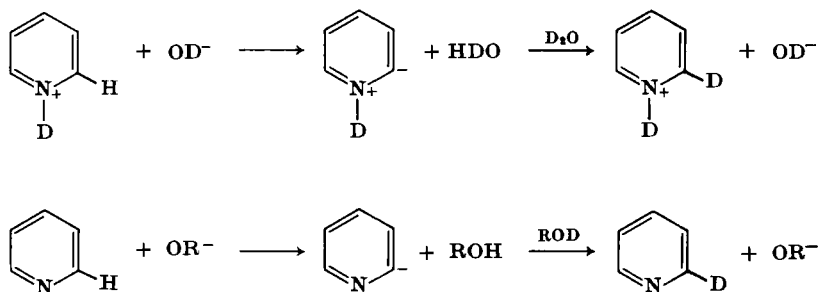
⁴⁸ J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.* **91**, 5501 (1969).

⁴⁹ J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.* **89**, 3358 (1967).

⁵⁰ I. F. Tupitsyn, N. N. Zatssepina, A. V. Kirova, and Yu. M. Kapustin, *Reakts. Sposobnost Org. Soedin.* **5**, 601 (1968).

bond, leading to decreased acidity whereas the small increase in s -character of the C(3)-H and C(4)-H bonds should be associated with an acidity increase. For comparison, a change from sp to sp^2 hybridization is equivalent to a 17% reduction in s -character; and in going from acetylene to ethylene there is a fall in acidity of 11 p*K* units. (2) Electrostatic repulsion between the coplanar nitrogen electron pair and the electron pair of the adjacent anion results in a destabilization of the latter and hence leads to a reduced acidity of the C(2)-H bond. The results of extended Hückel theory calculations⁵¹ suggest that this second factor is the more important of the two contributions.

In the aqueous pH region the mechanism for hydrogen-deuterium exchange in pyridine involves attack of deuteroxide ion on the pyridinium ion to give an ylide intermediate (Scheme 8). The ylide then reacts with D₂O to give the deuterated pyridine. In more basic media the proposed mechanism involves rate-determining deprotonation from the neutral molecule to give a carbanion intermediate which then abstracts a deuteron from the solvent (Scheme 9).



SCHEME 9

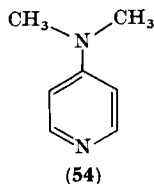
The effects of substituents in the pyridine ring on the rates of isotopic exchange have been studied.⁵² In general an electron-withdrawing group at the 3-position accelerates exchange at the 4-position while an electron-withdrawing group at the 4-position accelerates exchange at the 3(5)-position(s). In both cases exchange at positions adjacent to the nitrogen heteroatom (2,6) is more difficult relative to the other positions; this behavior is similar to that witnessed for pyridine itself. The observation⁵² that for 3-chloropyridine base-catalyzed isotopic exchange occurs readily at C-4 but not at C-2 accounts for the fact⁵³ that 3,4- but not 2,3-pyridynes are produced by dehydrohalogenation of 4-unsubstituted

⁵¹ W. Adam, A. Grimison, and R. Hoffmann, *J. Amer. Chem. Soc.* **91**, 2590 (1960).

⁵² J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.* **88**, 4766 (1966).

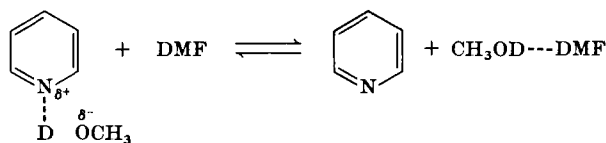
⁵³ H. J. den Hertog and H. C. Van der Plas, *Advan. Heterocycl. Chem.* **4**, 121 (1965).

3-halogenopyridines, although the relative stabilities favor the 2,3-pyridyne.⁵⁴



The base-catalyzed deuteration of 4-amino- and 4-*N,N*-dimethylaminopyridine (54) takes place at both the α - and β -positions, although that at the α -positions strongly predominates in the weakly alkaline solutions made by adding the amine to D_2O . The mechanism of the exchange at both positions is similar to that in other pyridines.⁵⁵

The solvent effect on the rates of isotopic exchange of substituted pyridines has also been investigated.⁵⁶ In going from CH_3OD to $CH_3OD-OCH_3$ the activation energy increases by 3–10 kcal mole⁻¹ although the rate of exchange is several powers of ten faster in the more basic medium. This suggests that different mechanisms are operative in the two media—attack of alkoxide ion on the pyridinium ion as opposed to deprotonation of the neutral base in the more basic medium. Addition of the dipolar aprotic solvent dimethylformamide (DMF) to a solution of CH_3OK in CH_3OD made little difference to the rate of isotopic exchange. This result was interpreted in terms of the desolvation of the pyridine molecule (Scheme 10). Because of the partial positive charge on the nitrogen the solvated pyridine molecule was the more reactive species and this effect was more important than that resulting from the increased basicity of the methoxide ion.



SCHEME 10

Evidence in favor of the existence of a carbanion intermediate in the isotopic exchange reactions of neutral pyridines comes from various

⁵⁴ H. L. Jones and D. L. Beveridge, *Tetrahedron Lett.* 1577 (1964).

⁵⁵ J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Lett.* 421 (1968).

⁵⁶ I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, and Yu. M. Kapustin, *Reakts. Sposobnost Org. Soedin.* 5, 806 (1968).

sources. Lithium derivatives of pyridine are known and undergo reactions characteristic of carbanions.⁵⁷ Reference has previously been made^{52, 53} to the likely existence of a carbanion intermediate in the dehydrohalogenation of 3-halopyridines in liquid ammonia. Finally, the observed correlation⁵⁰ between the rates of exchange at the meta and para positions of various 3- and 4-substituted pyridines and $\sigma_X^0 + \sigma_N^0$ where σ_X^0 is the Taft substituent constant for group X and σ_N^0 is the substituent constant for the ring nitrogen atom, indicates that inductive rather than resonance effects of substituents predominantly influence reactivity; the large positive ρ value (+5.0) shows that a considerable amount of negative charge (carbanion character) is generated in the transition state of these isotope exchange reactions. It is interesting that the same equation also correlates the rates of exchange at the meta and para positions of monosubstituted benzenes, so that a common mechanism for both benzenes and pyridines seems likely.

For isotopic hydrogen exchange in pyridinium salts the positional reactivity is considerably different from that exhibited by the pyridines and in several instances studies⁵⁸ have shed light on some unexpected orientations observed in a number of nucleophilic substitution and addition reactions⁵⁹ involving these species. For 3-methylpyridine methiodide (**55**), for example, in 0.1 *N* NaOD in D₂O the order of reactivity (2 > 6 > 4,5) is similar to that obtained for 3-cyanopyridine methiodide (2 > 6 > 4,5). From a study of the deuteration of 1-methylpyridinium chloride⁶⁰ at 165° in phosphate-buffered D₂O the 3(5)- and 4-positions were found to be less reactive than the 2(6)-position(s) by factors of 10³ and 3.4 × 10³, respectively. 1-Methylnicotinamide cation⁵⁹ (**56**) and 1-methylpyridinium chloride⁶¹ exchange the 2-H and 6-H in a solution of sodium carbonate in D₂O at 100°, the former exchange being the faster. The *N*-methyl hydrogens also exchange under the same conditions but approximately 300 times more slowly. The greater acidity of the ring α -protons compared to the *N*-methyl protons is usually ascribed to the hybridization differences at the carbon atoms. In all these exchanges a pyridinium ylide intermediate was invoked, **57** for exchange at the α -position and **58** for exchange in the methyl group. No possibility of *d*-orbital stabilization of the carbanions exists for these pyridinium salts.

⁵⁷ H. Gilman and S. M. Spatz, *J. Org. Chem.* **16**, 1485 (1951).

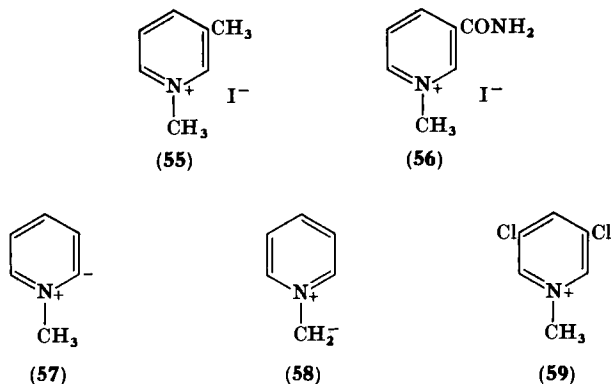
⁵⁸ R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.* **6**, 229 (1966).

⁵⁹ H. E. Dubb, M. Saunders, and J. H. Wang, *J. Amer. Chem. Soc.* **80**, 1767 (1958).

⁶⁰ J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *J. Amer. Chem. Soc.* **90**, 5939 (1968).

⁶¹ K. W. Ratts, R. K. Howe, and W. G. Phillips, *J. Amer. Chem. Soc.* **91**, 6115 (1969).

Deprotonation of the pyridinium ion (59) at positions α to the heteroatom has been studied⁶² using neutral and anionic buffer bases in D_2O . No catalysis other than by the deuteroxide ion was observed and once



again reaction is thought to proceed via the ylide intermediate. The observed correlation⁶³ between rates of deuteroxide-catalyzed H/D exchange at the equivalent 2- and 6-positions of various 1-substituted pyridinium ions and the Taft σ inductive parameter provides further evidence for the formation of such an intermediate. The magnitude of the activating effects of substituents are similar to those found for H/D exchange involving uncharged carbon acids. From a comparison of the rates of exchange for benzene, Zoltewicz *et al.*⁶³ calculate that a positively charged annular nitrogen atom activates an aromatic ring for deprotonation via ylide formation by a factor of 10^{14} – 10^{16} .

Base-catalyzed deprotonation of pyridine 1-oxides should occur much more readily than in the pyridines themselves and this prediction has been borne out by several workers.^{64, 65} These compounds exhibit the same relative positional reactivity as do the pyridinium ions. For example, for 3-bromopyridine 1-oxide⁶⁴ in 0.1 *N* NaOD– D_2O the order is $2 > 6 > 4 > 5$, as would be expected on the basis of the net ($\pi + \sigma$) electron densities at the various nuclear positions. For pyridine 1-oxide the relative rates of exchange in methanolic methoxide solutions⁶⁶ at 50° are

⁶² J. A. Zoltewicz, C. L. Smith, and G. M. Kauffman, *J. Heterocycl. Chem.* **8**, 337 (1971).

⁶³ J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.* **92**, 7547 (1970).

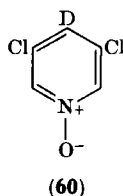
⁶⁴ R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.* **55** (1967).

⁶⁵ R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.* **89**, 1537 (1967).

⁶⁶ I. F. Tupitsyn, N. N. Zatssepina, Yu. M. Kapustin, and A. V. Kirova, *Reakts. Spooobnost Org. Soedin.* **5**, 613 (1968).

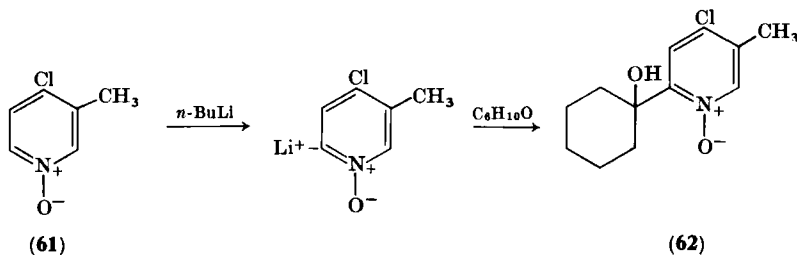
4:3:2-1.0:5.0:500 and are similar to the values obtained by Zoltewicz⁶⁷ at a higher temperature in the same medium, and also in $\text{NaNd}_2\text{-ND}_3$.⁶⁸

The effects of substituents on the rates of exchange of the 2-H of several pyridine 1-oxides have been investigated.⁶⁴ In all cases the rate increases with increasing electron-withdrawing power of the substituent although the effect is smaller when the substituent is at the C-4 position



rather than at C-3. The mechanism of the exchange is the same as that for pyridine and the pyridinium salts, namely, rate-determining deprotonation by the lyate ion to give a carbanion intermediate which then abstracts a deuteron from the solvent in a fast step to give the exchanged product; the dedeuteration of the pyridine *N*-oxide (60) at a position γ to the heteroatom was studied⁶² in order to obtain details of the reaction mechanism.

Considerable evidence for the existence of a carbanion intermediate in the isotopic exchange reactions of pyridine 1-oxides is available. Treatment of 4-chloro-3-methylpyridine 1-oxide (61), for example,⁶⁵ with *n*-butyllithium gives an intermediate which reacts with cyclohexanone to give 62. In addition Tupitsyn *et al.*⁶⁶ have found a linear



relationship between the logarithm of the rate constant for exchange at the 2-position of unsubstituted and 2-substituted pyridine 1-oxides and the Taft σ^* -substituent constant where σ^* includes $\sigma^*_{2\text{NO}} + \sigma^*_\text{X}$, X

⁶⁷ J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.* **34**, 1405 (1969).

⁶⁸ N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. I. Belyashova, *Reakts. Sposobnost Org. Soedin.* **6**, 257 (1969).

being the substituent. The value obtained for ρ (10.8) suggests a considerable amount of carbanion character in the transition state. Finally, the relative rates of exchange for pyridine 1-oxide parallel those for the decarboxylation of the isomeric *N*-methylpyridinium carboxylate betaines where an intermediate carbanion is known to exist.

Solvent effects for the exchange of pyridine 1-oxides have been investigated.⁶⁶ For exchange at the C-2 position of 3-fluoro- and 3-nitropyridine 1-oxide, the activation energy decreases in going from MeOD to MeOK–MeOD, exactly opposite to that found for neutral pyridines. Lower solvation of the pyridine 1-oxide as compared to the much more basic pyridine was the suggested explanation. Addition of the aprotic solvent dimethylformamide to MeOK–MeOD solutions increased the rates of exchange by between 3- and 30-fold so that the effect of increased basicity outweighed changes in solvation. Exchange of the 2,6-hydrogens of pyridine 1-oxide is twice as fast in MeOD as in MeOH, probably due to the higher basicity of the methoxide ion in the deuterium-containing solvent.

Base-catalyzed hydrogen–deuterium exchange occurs at the positions adjacent to the heteroatom for 1-methyl-2-pyridone⁶⁹ (**63**) and 1-methyl-4-pyridone⁷⁰ and not at the methyl group as has been suggested.⁶ Thus 1-methyl-4-pyridone in D₂O at 100° gives 1-methyl-4-pyridone-2,6-[²H] via an ylide mechanism. The rate of exchange is slower than for 4-thiapyrone (**64**), as expected if stabilization of the developing negative charge by *d*– σ overlap with sulphur is an important factor.

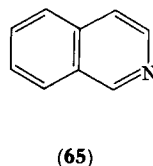
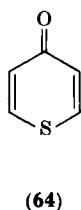
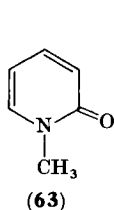
By comparison with the pyridines, considerably less work has been done on the kinetics of hydrogen exchange of the quinolines. Tupitsyn *et al.*⁶⁰ have found from studies in methanol–methoxide solutions at 180° that the positional reactivity is similar to that exhibited by pyridine. Furthermore the actual rates are about 2–3 times faster so that the inductive electron-withdrawing effect of the benzene ring must be operating. Isoquinoline (**65**) exchanges both the 4-H and 1-H at 160° in 0.6 *N* MeOK–MeOD, with the former being the more labile; no exchange for the 3-H was reported. Hydrogen exchange from both the 2-position of quinoline and the 1-position of iso-quinoline^{70a} proceeds by hydroxide-ion attack on the protonated molecules.

The most reactive position for base-catalyzed hydrogen exchange of the 1-oxide derivatives of quinoline and isoquinoline is the position adjacent to the heteroatom and nearest the fused benzene ring.⁵⁹ Thus for isoquinoline 1-oxide the positional reactivity is given by 1 > 3 > 4,

⁶⁹ P. Beak and E. M. Monroe, *J. Org. Chem.* **34**, 589 (1969).

⁷⁰ P. Beak and J. Bonham, *J. Amer. Chem. Soc.* **87**, 3365 (1965).

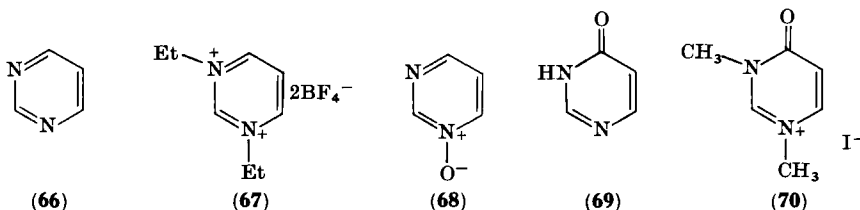
^{70a} U. Bressel, A. R. Katritsky, and J. R. Lea, *J. Chem. Soc. C*, 5 (1971).



while for quinoline 1-oxide in 0.1 *N* CH₃OK–CH₃OD only exchange from the 2-position has been observed. In 1,10-phenanthridine-1-oxide^{70b} the 2-position is similarly the most reactive.

B. CONTAINING TWO NITROGEN ATOMS

Pyrimidine (66) undergoes base-catalyzed exchange in methanolic methoxide solutions at high temperatures (160°–180°).^{48, 50} The positional reactivity is similar to that found for pyridine; the least reactive center is that between the two nitrogen atoms, and the most reactive is position 5. Little work has been done on isotopic exchange of pyrimidinium salts. For 1,3-diethylpyrimidinium difluoroborate (67), but not 1-ethylpyrimidinium fluoroborate, base-catalyzed exchange is reported to occur at the 2-position in CF₃COOD.⁷¹



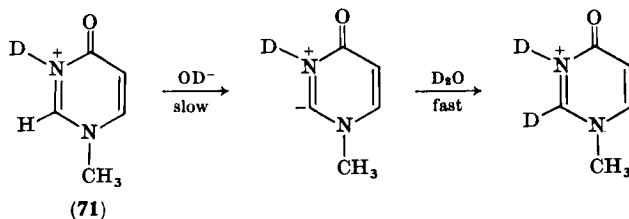
Pyrimidine *N*-oxide (68) has been successfully deuterated⁶⁶ in all positions in MeOK–MeOD, the positional reactivity being much as expected, in the order 2 > 6 > > 4 > > 5. 4-Pyrimidone (69) and a number of 1- and 3-alkyl-4-pyrimidones exchange their 2-H in D₂O at elevated temperatures;⁷² with different 1-alkyl groups the order of reactivity was Me > C₆H₅CH₂ > H. The rate of exchange of 3-methyl-4-pyrimidone was determined over a pD range and the mechanism deduced as probably involving attack by OD[–] on the pyrimidone cation. This interpretation is supported by the observation that exchange at the

^{70b} I. Fletcher, A. J. Boulton, and A. R. Katritzky, *J. Chem. Soc. C*, 1193 (1971).

⁷¹ T. J. Curphey, *J. Amer. Chem. Soc.* **87**, 2063 (1965).

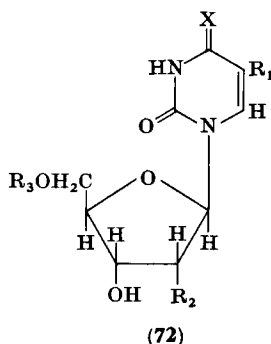
⁷² G. E. Wright, L. Bauer, and C. L. Bell, *J. Heterocycl. Chem.* **3**, 440 (1966).

2-position in 1,3-dimethyl-4-pyrimidonium iodide (**70**) is much faster than its unquaternized analog. The more recent work of Beak and Bonham⁷⁰ has confirmed that exchange of the 2-H of 1-methyl-4-pyrimidone takes place by deuteroxide-catalyzed attack on the pyrimidonium ion (**71**) leading to an ylide intermediate (Scheme 11).



SCHEME 11

Exchange of the 5-H of uridine (**72**, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{H}$, $\text{X} = \text{O}$) in slightly basic D_2O at 60° using 2-mercaptoethylamine as base has been reported.⁷³ Similar exchange was also observed in deoxyuridine (**72**, $R_1 = R_2 = R_3 = \text{H}$, $\text{X} = \text{O}$) and uridine monophosphate (**72**, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{PO}_3\text{H}_2$, $\text{X} = \text{O}$), and a probable mechanism involves a Michael 1,4-addition across the double bond followed by a tautomeric shift and then elimination of the C-5 hydrogen and the nucleophile. Exchange of the 5-H of uridine in the presence of ammonium sulfite at 37° proceeds best at pH 9. The mechanism involves deprotonation of the bisulfite-uridine complex by the ammonia or added amines.^{73a}



Quinazoline (**73**) is deuterated^{50, 73} in the 2- and 4-positions at a measurable rate at 160° in 0.6 *N* MeOK–MeOD and again the rate of

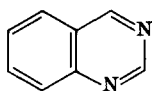
⁷³ S. R. Heller, *Biochem. Biophys. Res. Commun.* **32**, 998 (1968).

^{73a} I. Wataya and H. Hayatsu, *Biochemistry* **6**, 3583 (1972).

exchange is somewhat faster than at the analogous positions of pyrimidine. The large activating effect of the *N*-oxide function is illustrated by the fact that quinazoline 1,3-dioxide exchanges⁷⁴ at the 2- and 4-positions in MeOD at the much lower temperature of 65°.

Base-catalyzed hydrogen exchange in pyridazine (74) occurs in NaOD-D₂O⁷⁵ and MeONa-MeOD,⁵⁰ the positional reactivity being 4(5) > 3(6) in both cases. Once more the decreased reactivity of a center ortho to a nitrogen atom relative to a more removed center is evident; like pyridine, pyridazine does not have the regular geometry of benzene.

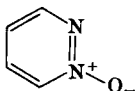
Pyridazine 1-oxide (75) exchanges its 6-H in NaOD-D₂O at room temperature and other hydrogens at successively higher temperatures,



(73)



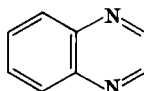
(74)



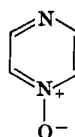
(75)



(76)



(77)



(78)

with the order of reactivity $6 > 5 > 3 > 4$.⁷⁵ For 3-hydroxypyridazine 1-oxide, the positional reactivity⁷⁶ is in the order $6 > 4 > 5$.

Pyrazine (76) was found to exchange all four equivalent hydrogens in 0.6 *N* MeOK-MeOD at high temperatures, while quinoxaline (77) exchanges its 2-H and 3-H under the same conditions and at approximately the same rate.⁵⁰ The catalyst was determined by Zoltewicz,⁴⁸ who found that the exchange was first order in methoxide ion. Pyrazine 1-oxide (78) exchanged at the 2(6)-position in 0.1 *N* MeOK-MeOD at room temperature, whereas a temperature of 130° was necessary to induce exchange at the 3(5)-position.⁶⁶ Pyrazine 1,4-dioxide exchanges all four equivalent hydrogens in MeOD at 65° while quinoxaline 1,4-dioxide exchanges its 2-H and 3-H at a slightly slower rate.⁷⁴

⁷⁴ I. F. Tupitsyn, N. N. Zatsepina, and A. V. Kirova, *Reakts. Sposobnost Org. Soedin* **5**, 626 (1968).

⁷⁵ Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.* **12**, 1384 (1964).

⁷⁶ H. Igeta, M. Yamada, Y. Yoshioka, and Y. Kawazoe, *Chem. Pharm. Bull.* **15**, 1411 (1967).

V. Discussion

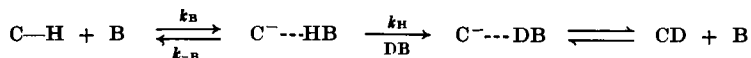
From the work already done on base-catalyzed hydrogen exchange in heterocyclic compounds a number of points emerge. First, the conditions necessary to induce exchange vary widely and may be dictated by structural features. In some cases reactions proceed very slowly even in highly basic media at elevated temperatures, while in others relatively fast base-catalyzed reactions occur in highly acidic media at low temperatures. Where necessary the rates of exchange may be increased by inserting additional electron-withdrawing substituents and/or more electronegative atoms close to the site of the exchanging proton. Several reactivity orders have, in fact, been constructed,^{12, 15} but these will be of limited value until more uniform reaction conditions are employed.

Second, the reactions differ from many proton-transfer reactions in that the negative charge is extensively localized and little solvent and structural reorganization is necessary in order that exchange may take place. Whereas the ionization of such carbon acids as ketones and nitro compounds involves considerable reorganization and is general-base-catalyzed, overwhelming hydroxide ion catalysis over a wide pH range is the generally observed behavior of heterocyclic compounds. The Brönsted exponent β is therefore close to unity and there is no reason to believe that it represents anything other than an accurate criterion of transition-state structure for these reactions. Although relatively few primary hydrogen isotope effects have been measured for heterocyclics, the values obtained (Table I) are all low, suggesting, like the β -values, that the transition states resemble closely the products. In fact the isotope effects are probably governed more by equilibrium than by kinetic factors. Kemp and O'Brien³⁴ have suggested that in such circumstances the characteristic eigenplot of $\log k$ vs. ΔpK will show an abnormally small pK region where neither forward or reverse rates are limiting. Isotope exchange reactions of heterocyclic compounds therefore resemble more closely those of oxygen rather than carbon acids. Molecular orbital calculations¹⁵ of cation-to-ylide deprotonation and of neutral molecule-to-anion deprotonation energies, assuming the transition state resembled the ylide or anion, predicted reactivities which were substantially correct. Zatsepina *et al.*³⁹ have performed similar calculations, and again, the assumption that the transition state is one in which the carbon-hydrogen bond is almost completely broken, gives a good correlation between observed exchange rates and the π -localization energies.

TABLE I
PRIMARY KINETIC HYDROGEN ISOTOPE EFFECTS IN THE BASE-CATALYZED EXCHANGE OF
VARIOUS HETEROCYCLIC COMPOUNDS

Compound	Position of exchange	k_H/k_T	k_D/k_T	Temperature	Basic system	References
Benzthiazole	H-2	—	1.1	0°	OEt ⁻ -EtOD	39
3-Methylthiazolium iodide	H-2	5.2	—	28°	OD ⁻ -D ₂ O	33
3-Benzyl 4,5-dimethyl- thiazolium bromide	H-2	2.7	—	30°	OH ⁻ -H ₂ O	34
3-Benzylbenzthiazolium bromide	H-2	4.8	—	30°	OH ⁻ -H ₂ O	34
<i>N</i> -Methylpyridinium iodide	H-2(6)	—	~ 1.0	55°	(C ₂ H ₅) ₃ N-MeOH	18
Purine	H-8	3.8	—	85°	OH ⁻ -H ₂ O	40

In view of the above, several workers, notably Zoltewicz,⁶³ have stressed the likely importance of the "internal return" mechanism^{77, 78} (Scheme 12) for proton-transfer reactions from heterocyclic compounds.



SCHEME 12

When carbon acids deprotonate in a step that involves considerable solvent and structural reorganization to give a resonance-delocalized anion the rate of back protonation (k_{-B}) is usually slow and less than k_H . Such acids exhibit general base catalysis and the primary hydrogen isotope effects usually fall in the range $k_H/k_D = 3-8$. However, when none of these factors is important the energy barrier for reprotonation is low and the rate of protonation of the hydrogen-bonded carbanion (k_{-B}) competes favorably with the rate of replacement of hydrogen by deuterium from the solvent at the carbanion site (k_H). The rate-limiting step is the separation of the hydrogen-bonded complex and this is preceded by an equilibrium. In these circumstances low primary hydrogen isotope effects and Brönsted β -exponents of unity are the rule. Clearly proton-transfer reactions from heterocyclic compounds provide a favorable situation for the operation of such a mechanism.

Many applications have resulted from studies of base-catalyzed isotope exchange reactions of heterocyclic compounds, not least being the ease with which labeled molecules can now be obtained. Thus, prior to the finding that purines labeled with either deuterium or tritium at the C-8 position could be prepared merely by heating in D_2O or HTO at $90^\circ-100^\circ$ for 10-20 minutes, it was customary to prepare the required compound by a modification of the classical method of Traube⁷⁹ involving ring closure of a selected pyrimidine. Likewise, heterogeneous methods of exchange,^{80, 81} often involving expensive catalysts, were widely used for incorporating tritium and deuterium into heterocyclic compounds.

For many of the compounds it is fortunate that isotopic exchange leads to specific labeling. Such compounds can subsequently be used for

⁷⁷ D. J. Cram, C. A. Kingsburg, and B. Rickborn, *J. Amer. Chem. Soc.* **83**, 3688 (1961).

⁷⁸ A. Streitwieser, A. Streitwieser, and H. F. Koch, *J. Amer. Chem. Soc.* **86**, 404 (1964).

⁷⁹ W. Traube, *Ber.* **33**, 1371 (1900).

⁸⁰ M. L. Eidinoff, H. C. Reilly, J. E. Knoll, and D. H. Marrian, *J. Biol. Chem.* **199**, 511 (1952).

⁸¹ D. G. Crowter, E. A. Evans, and R. Rasdell, *Chem. Ind. (London)*, 1622 (1962).

the assignment of NMR spectra.⁸² In addition, methods developed for base-catalyzed deuterium labeling at C-8 of purines and at C-6 and/or C-5 of pyrimidines have been applied to nucleosides, nucleotides, and dinucleoside phosphates.⁸³ Knowing the approximate rates of deuterium labeling of common nucleoside bases, it was possible to label each of the nucleoside bases selectively in the presence of the others. Thus because adenosine exchanges > 10 times as fast as cytidine at pD 5.4 and by an even greater factor near neutrality, the adenosine only can easily be labeled in a mixture of the two.

That the isotopic exchange procedure is potentially useful as a diagnostic tool for detection of minute traces of labeled compounds can be seen in the recently developed method⁸⁴ for assay of guanine residues in DNA. Methylation of the N-7 position of guanine derivatives renders the 8-H extremely labile so that exchange proceeds quite rapidly even under physiological conditions. The same behavior is observed after methylation of DNA specifically labeled with tritium in the C-8 position of guanine residues. In fact, the yield of HTO corresponds exactly to the yield of 7-methylguanine, and the method can be applied to the analysis of DNA after interaction with various drugs such as the antibiotic mitomycin C.⁸⁵

Finally, it is worth noting that although the rates of exchange of carbon-bound hydrogens are known to be affected by the electron density at adjacent atoms it is not always appreciated that the latter also depends on the conformation of the molecule in solution and consequently the accessibility of the solvent to exchangeable hydrogens.⁸⁶ Thus the rates of detritiation from adenine residues in polyadenylic acid, which exists in solution as single-strand helices with extensive base stacking (44% at 60°), is a factor of 4 less than the corresponding rates from adenosine 5'-monophosphate in the temperature range 20°–60°. At 90°, where the percentage of stacked bases is no higher than 15%, the rates are approximately the same.

ACKNOWLEDGMENT

Support for this work in the form of a grant from the Radiochemical Centre to one of the authors (C. O'B.) is gratefully acknowledged. We also thank the Director, Dr. W. P. Grove, for permission to publish some of the findings reported here.

⁸² M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'o, *J. Amer. Chem. Soc.* **86**, 696 (1964).

⁸³ W. Wechter, *Collect. Czech. Chem. Commun.* **35**, 2003 (1970).

⁸⁴ M. Tomasz, *Biochim. Biophys. Acta* **199**, 18 (1970).

⁸⁵ M. Tomasz, *Biochim. Biophys. Acta* **213**, 288 (1970).

⁸⁶ R. N. Maslova, E. A. Lesnick, and Ya. M. Varshavsky, *Biochem. Biophys. Res. Commun.* **34**, 260 (1969).

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1,2,3-Triazoles

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I. Introduction

The chemistry of 1,2,3-triazoles has been reviewed before,¹⁻³ the last review surveying the literature up to 1960. Since then, several new syntheses of triazoles have been introduced, and the established routes have been greatly extended. There has been considerable interest in

¹ F. R. Benson and W. L. Savell, *Chem. Rev.* **46**, 1 (1950).

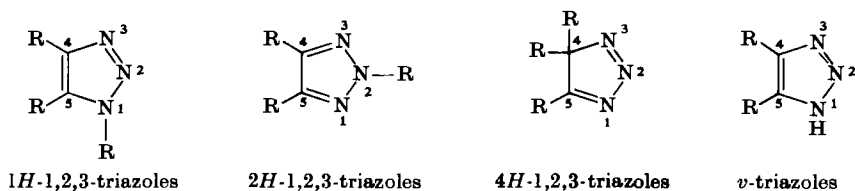
² E. Hoggarth, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4A, p. 439. Elsevier, Amsterdam, 1957.

³ J. H. Boyer, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 384. Wiley, New York, 1961.

1,2,3-triazoles as light stabilizers and as optical brightening agents, and also in their use as precursors for azapurines and similar heterocyclic systems, which are potential carcinostatic agents.

The present review, which surveys the literature to mid-1972, has been restricted to monocyclic 1,2,3-triazoles, since much of the chemistry of benzotriazoles and other fused systems has little in common with monocyclic triazole chemistry. The aim has been to give a broad survey of methods of synthesis and reactions of triazoles; few references are included from before 1960, as these are available from earlier reviews.

Nomenclature. Three classes of 1,2,3-triazoles can be recognized (Scheme 1); these are named as *1H*-, *2H*-, and *4H*-1,2,3-triazoles in *Chemical Abstracts*. Triazoles unsubstituted on nitrogen can be regarded either as *1H*- or as *2H*-derivatives, depending upon which tautomer is preferred. In *Chemical Abstracts* such compounds are classed as *v*-triazoles and are listed separately.



SCHEME 1

The first two classes can be regarded as aromatic systems whereas the third, the *4H*-system, cannot: This is reflected in the abundance of examples of *1H*- and *2H*-triazoles and the rarity of *4H*-triazoles.

II. Synthesis of the Triazole Ring

Most of the important general methods of forming *1H*-triazole derivatives involve azides; several reviews discuss aspects of the formation of triazoles in this way.^{4, 5} α -Diketones are also important precursors of both *1H*- and *2H*-triazoles. Triazoles unsubstituted on nitrogen can be prepared by the direct addition of hydrazoic acid or of azide ion, but it is often more convenient to obtain these compounds by removal of a substituent from a *1H*- or *2H*-substituted triazole (Section IV, E).

⁴ G. L'abbé, *Chem. Rev.* **69**, 345 (1969); T. Sheradsky, in "The Chemistry of the Azido Group" (S. Patai, ed.), p. 331. Wiley (Interscience), New York, 1971.

⁵ G. L'abbé, *Ind. Chim. Belg.* **34**, 519 (1969).

A. FROM AZIDES AND ACETYLENES

The thermal cycloaddition of azides to acetylenes is the most versatile route to 1*H*-1,2,3-triazoles, because of the wide range of substituents that can be incorporated into the acetylene and azide components. The accepted mechanism for the reaction is a concerted 1,3-dipolar cycloaddition.^{6,7} The rates of addition of phenyl azide to several acetylenes have been measured;⁷ the rates of formation of the aromatic triazoles are not appreciably different from the rates of cycloaddition to the corresponding olefins, indicating that the transition-state energy is not lowered significantly by the incipient generation of an aromatic system.

Although the method can, in principle, be applied to any combination of azides and acetylenes, it suffers from some disadvantages as a preparative procedure. Many reactions require elevated temperatures, which may be close to the decomposition temperature of the azide. Such reactions should be carried out on a small scale and at high dilution, since some azides, especially cyanogen azide and the lower alkyl azides, are unpredictably explosive.^{8,9} If thermal decomposition of the azide to the nitrene does become a competing reaction pathway (as happens, for example, with ethoxycarbonyl azide¹⁰), products of nitrene addition may be isolated. Although the triazole ring system is resistant to thermal cleavage, migration of substituents (especially acyl and trimethylsilyl groups, Section IV, C) from the 1- to the 2-position may be a complicating feature of thermal cycloaddition of azides.

Another problem with this method of synthesis is that unsymmetrical acetylenes can, and usually do, give two isomeric triazoles (Scheme 2). The sterically less hindered isomer is by no means always the major product: In addition to phenylacetylene, for example, the 5-phenyl-triazole often predominates in the product mixture.¹¹⁻¹³

Few unsymmetrical acetylenes give exclusively one isomer. Ynamines are exceptional in that they are reported to give solely the isomer with

⁶ R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *Chem. Ber.* **98**, 4014 (1965).

⁷ R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.* **100**, 2494 (1967).

⁸ F. Moulin, *Helv. Chim. Acta* **35**, 167 (1952).

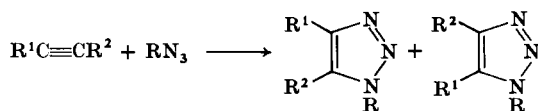
⁹ J. H. Boyer, R. Moriarty, B. de B. Darwen, and P. A. S. Smith, *Chem. Eng. News* **42**, 6 (1964).

¹⁰ R. Huisgen and H. Blaschke, *Chem. Ber.* **98**, 2985 (1965).

¹¹ G. L'abbé and A. Hassner, *Bull. Soc. Chim. Belg.* **80**, 209 (1971).

¹² G. Alonso, M. T. Garcia-López, G. Garcia-Muñoz, R. Madroñero, and M. Rico, *J. Heterocycl. Chem.* **7**, 1269 (1970).

¹³ L. Horner and W. Kirmse, *Ann.* **614**, 1 (1958).



SCHEME 2

the substituted amino group in the 5-position,¹⁴⁻²⁰ although the adducts with acyl azides may isomerize in the reaction conditions.^{20a} Regiospecific addition of ethoxyacetylene to alkyl and aryl azides has also been observed,^{21, 22} but addition to ethoxycarbonyl azide^{20a} and to glycosyl azides²³ gives both isomers. The only reported case of addition of an azide to 1-ethylthio-2-phenylacetylene appears to give only the 4-ethylthiotriazole.²³ In general, addition to unsymmetrical acetylenes tends to give mainly the isomers with electron-withdrawing groups at the 4-position and electron-releasing groups at the 5-position.²⁴⁻²⁶

A very bulky group, such as trimethylsilyl, tends to occupy the 4-position. Addition of phenyl azide to phenyltrimethylsilylacetylene gives almost exclusively the 4-trimethylsilyltriazole.²⁷ This can be useful because of the ease of removal of trimethylsilyl substituents. Additions to diacetylenes^{28, 29} and addition of *p*-diazidobenzene to 1,4-diethynylbenzene³⁰ are also claimed to be regiospecific.

Another method of achieving regiospecific addition to terminal

¹⁴ Union Carbide Corp., Netherlands Appl. 6,507,886 (1965) [*Chem. Abstr.*, **64**, 19630e (1966)].

¹⁵ R. E. Harmon, F. Stanley, S. K. Gupta, and J. Johnson, *J. Org. Chem.* **35**, 3444 (1970).

¹⁶ G. Himbert and M. Regitz, *Chem. Ber.* **105**, 2963, 2975 (1972); *Synthesis*, 571 (1972).

¹⁷ H.-J. Gais, K. Hafner, and M. Neuenschwander, *Helv. Chim. Acta* **52**, 2641 (1969).

¹⁸ R. E. Harmon, R. A. Earl, and S. K. Gupta, *J. Org. Chem.* **36**, 2553 (1971).

¹⁹ K. D. Berlin, S. Rengaraju, T. E. Snider, and N. Mandava, *J. Org. Chem.* **35**, 2027 (1970); D. Seyferth and P. Hilbert, *Org. Prep. Proced. Int.* **3**, 51 (1971).

²⁰ R. Buijle, R. Fuks, and H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **5**, 585 (1966).

^{20a} P. Ykman, G. L'abbé, and G. Smets, *Chem. Ind. (London)*, 886 (1972).

²¹ E. Fabbri, P. Vita Finzi, and P. Grünanger, *Gazz. Chim. Ital.* **90**, 413 (1960).

²² P. Vita Finzi and C. Scotti, *Atti Accad. Naz. Lincei, Rend., CiSci. Fis., Mat. Nat.* **41**, 204 (1966); *Chem. Abstr.* **67**, 54080 (1967).

²³ R. E. Harmon, R. A. Earl, and S. K. Gupta, *Chem. Commun.* 296 (1971).

²⁴ J. C. Sheehan and C. A. Robinson, *J. Amer. Chem. Soc.* **73**, 1207 (1951).

²⁵ G. L'abbé, J. E. Galle, and A. Hassner, *Tetrahedron Lett.*, 303 (1970).

²⁶ S. Corsano and R. Inverardi, *Ric. Sci.* **29**, 74 (1959); *Chem. Abstr.* **53**, 17108 (1959).

²⁷ L. Birkofer, A. Ritter, and H. Uhlenbrauck, *Chem. Ber.* **96**, 3280 (1963).

²⁸ A. Dornow and K. Rombusch, *Chem. Ber.* **91**, 1841 (1958).

²⁹ W. G. Finnegan and W. P. Norris, *J. Org. Chem.* **31**, 3292 (1966).

³⁰ Y. Gilliams and G. Smets, *Makromol. Chem.* **117**, 1 (1968).

acetylenes is to use the Grignard derivative or the acetylide in place of the acetylene. Such reactions, which are carried out in mild conditions, give the 5-substituted triazoles; additional substituents can be incorporated at the 4-position through the organometallic intermediate. As the mechanism of these additions is probably different from that in the normal acetylene reactions, the method is discussed separately at the end of this section.

Until recently it was often difficult to assign structures to the isomeric triazoles formed in additions to acetylenes. There are now several useful NMR criteria (Section III, B) which can help to distinguish the isomers.

1. *Aryl Azides*

Phenyl azide and its derivatives have been added to a wide range of acetylenes. Typical conditions involve heating the components in toluene for 2–24 hours.^{8, 13, 14, 21, 24, 26–28, 31} Addition to acetylene can be effected in acetone solution;³² cycloalkynes have also been generated *in situ* and reacted with phenyl azide.³³ With acetylenes carrying electron-withdrawing groups the rate of addition is marginally increased by an electron-releasing substituent in the azide, as might be expected for a concerted reaction. The addition of hexafluorohexa-2,4-diyne to *p*-dimethylaminophenyl azide proceeds under unusually mild conditions²⁹ (in Freon solution at room temperature for 2 hours), demonstrating the enhancement of reactivity provided by the electron-withdrawing trifluoromethyl groups and the electron-releasing *p*-dimethylamino group.

2. *Alkyl Azides*

Relatively few additions of the lower molecular weight alkyl azides have been performed, mainly because of their volatility and thermal sensitivity; simple alkyltriazoles are normally obtained by alkylation of the *v*-triazoles. On the other hand, a very wide range of less volatile substituted alkyl azides has been added to acetylenes: Their addition to acetylenic esters usually proceeds readily and provides a useful method of characterizing the azides. Benzyl azide has often been used because it is relatively stable (up to 150°), it is readily prepared, and the benzyl group can be removed from the resulting triazoles (Section IV, E).

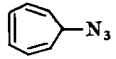
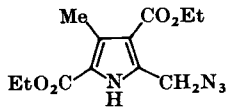
Table I contains a selection of examples of alkyl azide additions.

³¹ P. A. S. Smith and J. G. Wirth, *J. Org. Chem.* **33**, 1145 (1968).

³² D. S. Deorha, V. K. Mahesh, and S. K. Mukerji, *J. Indian Chem. Soc.* **40**, 901 (1963).

³³ G. Wittig and A. Krebs, *Chem. Ber.* **94**, 3260 (1961).

TABLE I
EXAMPLES OF ADDITION OF ALKYL AZIDES TO ACETYLENES

Azide	Acetylene	Conditions	Yield (%)	References
EtN ₃	PhC≡CH	130°, 13 hr	24	34
PhCH=CHN ₃	HC≡CCO ₂ Me	20°	62	25
PhCH ₂ N ₃	HC≡CCO ₂ H	50°, 24 hr	65	36
PhCH ₂ N ₃	PhC≡CPh	150°, 0.5 hr	95	35
PhCH ₂ N ₃	HOCH ₂ C≡CCH ₂ OH	115°, 7 hr	48	36
PhOCH ₂ N ₃	PhC≡CH	108°, 12 hr	70	38
EtOCOCH ₂ N ₃	HC≡CCH ₂ OH	78°, 96 hr	—	39
R ₂ C(NO ₂)N ₃	HC≡CH	70°, 135 hr	30	40
MeC(NO ₂) ₂ CH ₂ N ₃	HC≡CCO ₂ H	20°, 72 hr	90	43
CNCH ₂ N ₃	HC≡CH	100°, 5 hr	98	41
	PhCOC≡CCOPh	80°, 2 hr	58	37
	MeO ₂ CC≡CCO ₂ Me	80°, 0.5 hr	95	42

³⁴ R. Gompper, *Chem. Ber.* **90**, 382 (1957).

³⁵ R. Huisgen and M. Seidel, *Chem. Ber.* **94**, 2509 (1961).

³⁶ V. M. Brusnikina, S. S. Novikov, and V. A. Rudenko, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk.*, 474 (1961); *Chem. Abstr.* **55**, 23504 (1961).

³⁷ J. J. Looker, *J. Org. Chem.* **30**, 638 (1965).

³⁸ G. Garcia-Muñoz, R. Madroñero, M. Rico, and M. C. Saldana, *J. Heterocycl. Chem.* **6**, 921 (1969).

³⁹ C. F. Horn, U.S. Patent 3,324,085; *Chem. Abstr.* **67**, 44802 (1967).

⁴⁰ S. Maffei and G. F. Bettinetti, *Ann. Chim. (Rome)* **47**, 1286 (1957); *Chem. Abstr.* **52**, 7292g (1958).

⁴¹ H. Gold, *Ann* **688**, 205 (1965).

⁴² A. Treibs and K. Jacob, *Ann* **737**, 176 (1970).

⁴³ H. G. Adolph, *J. Org. Chem.* **36**, 806 (1971).

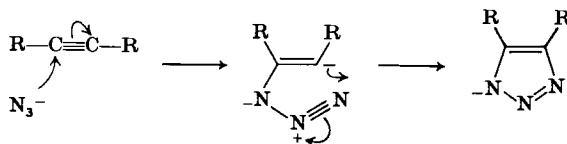
3. Trimethylsilyl Azide

Although high temperatures are required to effect the addition of trimethylsilyl azide to acetylenes, the azide is thermally stable, and good yields of triazoles are usually obtained.^{27, 44, 45} Typical conditions involve heating the components at 150°–170° for 6–20 hours. The products are always 2-trimethylsilyltriazaoles, indicating that migration of the trimethylsilyl group from N-1 to N-2 has occurred. The triazoles are readily desilylated to give the parent *v*-triazaoles.

4. Hydrazoic Acid and Sodium Azide

Hydrazoic acid adds readily to acetylenes with electron-withdrawing groups, and less readily to alkyl and aryl acetylenes.^{24, 46} Acetylene itself gives a high yield of *v*-triazole under carefully controlled conditions.⁴⁷ Not all acetylenes give triazoles with hydrazoic acid. Open-chain azides have been obtained with ethoxyacetylene and with dimethyl acetylenedicarboxylate.⁴⁸

Sodium azide in dimethylformamide or in dimethyl sulfoxide has been added to several acetylenes, although good yields are obtained only with acetylenes bearing electron-withdrawing groups.^{49, 50} Reactions involving azide ions are unlikely to follow the concerted 1,3-dipolar cycloaddition pathway; a mechanism involving nucleophilic addition to the triple bond, followed by 1,5-dipolar cyclization of the resulting vinyl anion, appears to be more likely (Scheme 3).



SCHEME 3

⁴⁴ L. Birkofer, A. Ritter, and P. Richter, *Chem. Ber.* **96**, 2750 (1963).

⁴⁵ L. Birkofer and A. Ritter, *Angew. Chem. Int. Ed. Engl.* **4**, 417 (1965); L. Birkofer and P. Wegner, *Chem. Ber.* **99**, 2512 (1966).

⁴⁶ A. Ayata, T. Mizoguchi, and S. Yamada, *Yakugaku Zasshi* **77**, 452 (1957) [*Chem. Abstr.* **51**, 14697 (1957)].

⁴⁷ A. Catino, *Ann. Chim. (Rome)* **58**, 1507 (1968) [*Chem. Abstr.* **70**, 87698 (1969)].

⁴⁸ M. E. C. Biffen, J. Miller, and D. B. Paul, in "The Chemistry of The Azido Group" (S. Patai, ed.), p. 130. Wiley (Interscience), New York, 1971.

⁴⁹ F. P. Woerner and H. Reimlinger, *Chem. Ber.* **103**, 1908 (1970).

⁵⁰ A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR* **158**, 408 (1964).

5. Sulfonyl Azides

Toluene-*p*-sulfonyl azide adds to electron-deficient acetylenes and to phenylacetylene at 80°–100° over a period of several days.⁵ The azide adds much more readily to ynamines,^{14, 15, 16} reflecting the electronic compatibility of these components. The triazoles so formed are labile and exist in equilibrium with open-chain diazo tautomers (Section IV, G); the adduct with ethoxyacetylene exists entirely in the diazo form.^{16, 51} Other sulfonyl azides have been reacted with arylacetylenes, but yields of triazoles are generally poor.⁵²

6. Cyanogen Azide

Cyanogen azide is less stable than most azides, and few additions have been attempted. Addition to acetylene and to alkynes gives the triazoles,⁵³ which, like some sulfonyl triazoles, exist in equilibrium with open-chain tautomers.

7. Acyl and Alkoxy carbonyl Azides

In general, acyl azides are too unstable to survive at the temperatures required for addition to acetylenes, although benzoyl azide adds readily to ynamines in toluene.^{14, 20a} Ethoxycarbonyl azide also gives triazoles in good yield with ynamines.^{17, 20a} The azide adds to propargylic alcohols in boiling ethanol,⁵⁴ and to acetylene at 100° under pressure.⁴¹ Addition to phenylacetylene and to electron-deficient acetylenes has been carried out at 130°.¹⁰ Oxazoles are also formed at this temperature by competing thermal decomposition of the azide, and addition of ethoxycarbonylnitrene to the acetylenes. The triazole obtained from phenylacetylene is 2-ethoxycarbonyl-4-phenyltriazole; the two 1-ethoxycarbonyltriazoles can be isolated if the addition is carried out at 50° over several weeks.⁵⁵ Since the 1*H*- to 2*H*-triazole isomerization takes place readily in these systems, a 1*H*-structure cannot be assumed for a triazole formed by addition of these azides.

8. Other Azides

Additions to acetylenes have been carried out with many other types of azide, including glycosyl azides,^{12, 18} various heterocyclic azides⁵⁶

⁵¹ P. Grünanger, P. Vita Finzi, and C. Scotti, *Chem. Ber.* **98**, 623 (1965).

⁵² P. Vita Finzi, *Chim. Ind. (Milan)* **47**, 1338 (1965).

⁵³ M. E. Hermes and F. D. Marsh, *J. Amer. Chem. Soc.* **89**, 4760 (1967).

⁵⁴ H. A. Stansbury, J. A. Durden, and W. H. Catlette, US Patent 3,161,651 [*Chem. Abstr.* **62**, 10443g (1965)].

⁵⁵ P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron Lett.*, 5225 (1970).

⁵⁶ E. Gudriniece and V. Urbans, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **82** (1971) [*Chem. Abstr.* **74**, 125600 (1971)].

including 4-azidoquinoline,⁵⁷ and tetrazolopyridines and -pyrimidines⁵⁸ (which exist in tautomeric equilibrium with open azide forms), phosphorus azides,¹⁹ and organometallic azide derivatives of iron,⁵⁹ tin,^{60, 60a} and lead.⁶¹ Acetylenic azides, $\text{HC}\equiv\text{C}-\text{X}-\text{N}_3$ (where X is CH_2 , C_6H_4 , or $\text{CH}_2\text{CO}_2\text{CH}_2$), have been polymerized to give polytriazoles.⁶² Polytriazoles have also been prepared from polyvinyl chloride by reaction with sodium azide, and addition of the polyazide to phenylacetylene.⁶³

9. Azides and acetylenic Grignard Reagents or Acetylides

Alkyl,⁶⁴ aryl^{64, 65} and sulfonyl⁶⁶ azides have been observed to form triazole derivatives with organolithium and organomagnesium derivatives of terminal acetylenes. The triazole structures proposed³ for the products of the reaction of *p*-toluenesulfonyl azide with sodium phenylacetylide have been modified after a reinvestigation of the reaction.⁵² Additions are carried out at 0° or below, and the mildness of the conditions suggests that the mechanism of the reaction may be different from that of normal azide additions. A plausible route (Scheme 4) involves nucleophilic attack of the acetylenic anion on the terminal nitrogen of the azide, followed by 1,5 anionic cyclization to give the triazolyl anion. The regiospecificity of the reaction supports this interpretation. The triazol-4-yl anion so formed can be carboxylated or can react with more azide to give a linear triazene; this in turn can be hydrolyzed or can be cleaved to give a diazonium salt, which couples with β -naphthol.⁶⁶ The method appears capable of further extension as a synthetic route.

⁵⁷ T. Itai and S. Kamiya, *Chem. Pharm. Bull.* **9**, 87 (1961) [*Chem. Abstr.* **55**, 27338 (1961)].

⁵⁸ R. Huisgen, K. v. Fraunberg, and H. J. Sturm, *Tetrahedron Lett.*, 2589 (1969); T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron* **27**, 5121 (1971); *J. Org. Chem.* **36**, 446 (1971).

⁵⁹ D. E. Bublitz, *J. Organometal. Chem.* **23**, 225 (1970).

⁶⁰ J. G. A. Luijten and G. J. M. van der Kerk, *Rec. Trav. Chim.* **83**, 295 (1964).

^{60a} S. Kozima, T. Itano, N. Mihara, K. Sisido, and T. Isida, *J. Organometal. Chem.* **44**, 117 (1972).

⁶¹ H. Gorth and M. C. Henry, *J. Organometal. Chem.* **9**, 117 (1967).

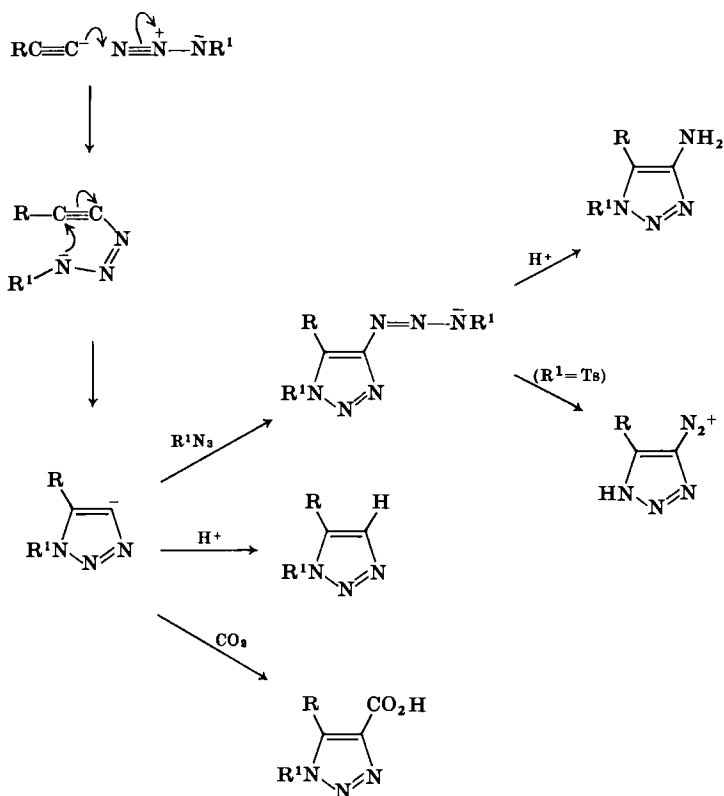
⁶² M. G. Baldwin, K. E. Johnson, J. A. Lovinger, and C. O. Parker, *J. Polymer Sci., Part B*, **5**, 803 (1967).

⁶³ M. Takeishi and M. Okawara, *J. Polymer Sci., Part B*, **8**, 829 (1970).

⁶⁴ G. S. Akimova, V. N. Chistokletov, and A. A. Petrov, *Zh. Org. Khim.* **3**, 968 (1967) [*Chem. Abstr.* **67**, 100071 (1967)]; **3**, 2241 (1967) [*Chem. Abstr.* **68**, 87243 (1968)].

⁶⁵ G. S. Akimova, V. N. Chistokletov, and A. A. Petrov, *Zh. Org. Khim.* **1**, 2077 (1965) [*Chem. Abstr.* **64**, 9713 (1966)]; *ibid.* **3**, 968 (1967) [*Chem. Abstr.* **67**, 100071 (1967)]; *ibid.* **4**, 389 (1968) [*Chem. Abstr.* **68**, 105100 (1968)].

⁶⁶ E. Robson, J. M. Tedder, and B. Webster, *J. Chem. Soc.*, 1863 (1963).



SCHEME 4

B. FROM AZIDES AND ACTIVATED METHYLENE COMPOUNDS

The base-catalyzed condensation of azides with activated methylene compounds is a well-established route to 1*H*-triazoles. In particular, it is the best route to triazoles bearing a 5-amino or hydroxy substituent and an aryl or carbonyl-containing function in the 4-position. The addition is regiospecific. The reaction is a stepwise one, since anomerism of glycosyl azides has been observed in their reaction with activated methylene compounds, indicating the presence of an intermediate.⁶⁷ The mechanism can be envisaged as a nucleophilic attack by the carbanion on the terminal nitrogen of the azide, followed by cyclization to a

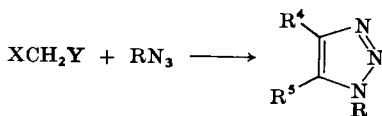
⁶⁷ R. L. Tolman, C. W. Smith, and R. K. Robins, *J. Amer. Chem. Soc.* **94**, 2530 (1972).



SCHEME 5

triazoline and aromatization (Scheme 5). In the reaction of azides with aliphatic ketones, the proposed intermediates have been detected in solution or isolated.⁶⁸

In accord with this mechanism, the reaction goes least readily with azides bearing electron-releasing groups. Benzyl azide has frequently been used because the benzyl group can be removed from the product. The reactions are usually carried out with alkoxides in alcohols or in tetrahydrofuran at room temperature or under reflux, using stoichiometric quantities of the reagents; the triazoles are often obtained in high yields. In most cases, the activated methylene group is flanked on both sides by electron-withdrawing substituents (although ethyl acetate and acetophenone have also been used successfully).¹ Thus, cyclization could take place in two different ways; in practice, however, cyclization almost invariably takes place in one direction. When one of the activating groups is a nitrile, cyclization takes place onto the nitrile carbon, leading to the formation of 5-aminotriazoles (an exception is found with α -cyanoacetophenone, which gives 4-cyano-5-phenyltriazoles).⁶⁹ When one of the activating groups is ethoxycarbonyl, cyclization always involves the other activating group and leads to the formation of 4-ethoxycarbonyltriazoles or the corresponding acids.



SCHEME 6

Representative examples of triazole syntheses (Scheme 6) involving the anions of activated methylene compounds are given in Table II.

Anomalous products have been noted with acetophenone, with malonodinitrile,^{70, 76} with malonodiamide and substituted malon-

⁶⁸ C. E. Olsen and C. Pedersen, *Tetrahedron Lett.*, 3805 (1968).

⁶⁹ S. Maiorana, *Ann. Chim. (Rome)* **56**, 1531 (1966); *Chem. Abstr.* **67**, 32420 (1967).

⁷⁰ J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.* **78**, 5832 (1956).

TABLE II
EXAMPLES OF ADDITION OF AZIDES TO ACTIVATED METHYLENE COMPOUNDS (SCHEME 6)

X	Y	R	R ⁴	R ⁵	Yield (%)	References
Ph	CN	<i>n</i> -C ₆ H ₁₃	Ph	NH ₂	98	72
Ph	CN	PhCH ₂	Ph	NH ₂	78	72, 77
Ph	CN	Me ₃ CCH=CH	Ph	NH ₂	91	75
Ph	CN	Ph	Ph	NH ₂	92	71
Ph	CN	MeSCH ₂	Ph	NH ₂	15	38
CONH ₂	CN	Ph	CONH ₂	NH ₂	88	73
CONH ₂	CN	<i>p</i> -NO ₂ -C ₆ H ₄	CONH ₂	NH ₂	97	73
CONH ₂	CN	Me	CONH ₂	NH ₂	7	73
CONH ₂	CN	PhCH ₂	CONH ₂	NH ₂	81	70
CN	CN	<i>p</i> -Cl-C ₆ H ₄	CN	NH ₂	~ 100	73
CO ₂ Me	CN	Me ₃ CCH=CH	CO ₂ Me	NH ₂	29	75
COMe	CO ₂ Et	CH ₂ =CPh	CO ₂ H	Me	72	75
COPh	CO ₂ Et	CH ₂ =CPh	CO ₂ H	Ph	69	75
CO ₂ Et	CO ₂ Et	PhCH ₂	CO ₂ Et	OH	48	70
COMe	CO ₂ Et	<i>p</i> -I-C ₆ H ₄	CO ₂ H	Me	94	74

⁷¹ E. Lieber, T.-S. Chao, and C. N. R. Rao, *J. Org. Chem.* **22**, 654 (1957); *Org. Synth.* **37**, 26 (1957).

⁷² E. Lieber, C. N. R. Rao, and T. V. Rajkumar, *J. Org. Chem.* **24**, 134 (1959).

⁷³ A. Dornow and H. Hell, *Chem. Ber.* **93**, 1998 (1960).

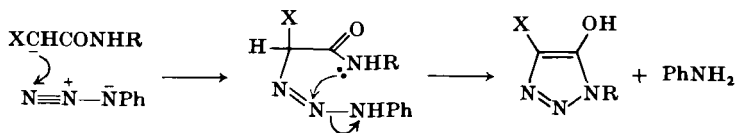
⁷⁴ H. Bojarska-Dahlig, *Rec. Trav. Chim.* **80**, 1348 (1961).

⁷⁵ G. L'abbé and A. Hassner, *J. Heterocycl. Chem.* **7**, 361 (1970).

⁷⁶ D. R. Sutherland and G. Tennant, *J. Chem. Soc. C*, 706 (1971).

⁷⁷ D. R. Sutherland and G. Tennant, *J. Chem. Soc. C*, 2156 (1971).

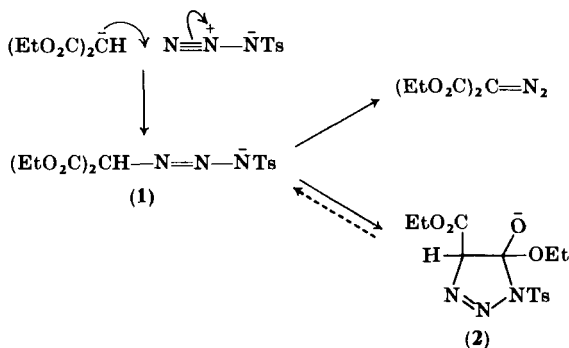
amides,⁷⁸ and with substituted malonic esters.⁷⁹ In the reaction of phenylacetonitrile with *o*-nitrophenyl azide and with *o*-azidobenzoic acid, the 5-aminotriazole reacts further by condensation of the amino group with the ortho substituents on the 1-phenyl group, resulting in the formation of fused triazoles.⁸⁰ Malonamides and phenylacetamide give an unusual reaction with phenyl azide from which triazoles are isolated which no longer contain an *N*-phenyl group;⁷⁸ aniline is also formed. A mechanism has been suggested involving cyclization of the triazene intermediate with displacement of aniline (Scheme 7).



SCHEME 7

With malonic esters and amides substituted at the central carbon, triazole formation is accompanied by decarboxylation and 4-alkyl- or 4-aryl-5-hydroxytriazoles are isolated.⁷⁹

Sulfonyl azides are exceptional in that they do not normally give triazoles with activated methylene compounds; nucleophilic attack by the carbanion is usually followed by loss of the sulfonamide anion, giving a diazo compound as the product.^{80a} Possible mechanisms for the reaction are illustrated (Scheme 8) for diethyl malonate. Attack of the carbanion on the terminus of the azide gives the anion of the linear triazene (1).



SCHEME 8

⁷⁸ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **18**, 1333 (1964).

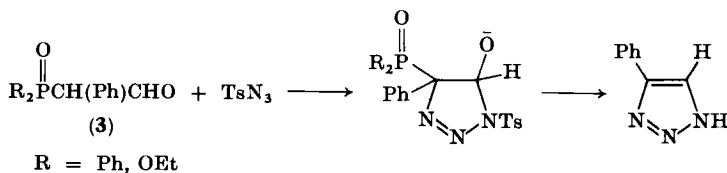
⁷⁹ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **23**, 1091 (1969).

⁸⁰ G. Tennant, *J. Chem. Soc. C*, 2290 (1966); 1279 (1967).

^{80a} M. Regitz, *Angew. Chem. Int. Ed. Engl.* **6**, 733 (1967).

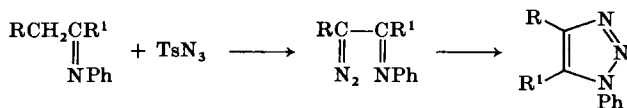
The toluene-*p*-sulfonamido anion may be lost from this, giving the diazo compound directly, or ring closure (which may be reversible) can take place, giving the triazoline anion (2).

Closure to the triazoline certainly occurs in many systems, since products are isolated which can only have been formed by this route.^{80a} Occasionally these products include *v*-triazoles; for example, 4-phenyl-triazole is isolated in moderate yield from the reaction of the aldehydes (3) with toluene-*p*-sulfonyl azide (Scheme 9).⁸¹



SCHEME 9

Triazoles have also been obtained when the carbon atom adjacent to the activated methylene group carries a nitrogen function (i.e., amides,⁸¹ nitriles,^{80a} amidines,⁸² and imines^{80a, 83}). In many of these cases it is impossible to decide, without ¹⁵N-labeling experiments, whether the third nitrogen of the triazole ring is derived from the toluene-*p*-sulfonyl azide or from the activated methylene compound. With amides, amidines, and nitriles, the first possibility seems more reasonable, but with imines, the third nitrogen is that of the imino group (Scheme 10).^{80a, 83}



SCHEME 10

From Azides and Alkoxides

Phenyl azide reacts with primary alkoxides to give 1-phenyltriazole derivatives.^{3, 84} Two moles of azide are required, the second being reduced to aniline. No mechanism has been proposed for the reaction;

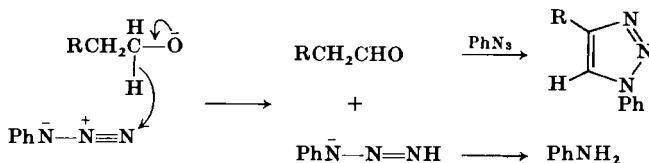
⁸¹ M. Regitz, W. Anschütz, and A. Liedhegener, *Chem. Ber.* **101**, 3734 (1968); M. Regitz and W. Anschütz, *ibid.* **102**, 2216 (1969).

⁸² J. Schawartz, M. Hornyák, and T. Süts, *Chem. Ind. (London)*, 92 (1970).

⁸³ M. Regitz, *Tetrahedron Lett.*, 3287 (1965); *Angew Chem. Int. Ed. Engl.* **4**, 431 (1965).

⁸⁴ H. El Khadem, H. A. R. Mansour, and M. H. Meshreki, *J. Chem. Soc. C*, 1329 (1968).

it possibly involves hydride transfer to 1 mole of phenyl azide, followed by attack of the carbanion of the aldehyde so produced on a second mole of the azide (Scheme 11).

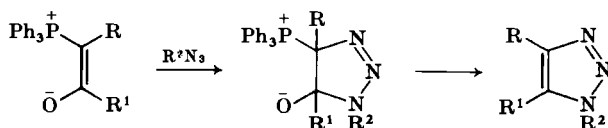


SCHEME 11

C. OTHER ROUTES INVOLVING AZIDES

1. From Azides and α -Acylphosphorus ylids

Addition of azides to α -acylphosphorus ylids takes place at room temperature in dichloromethane or at 80°C in benzene, giving triazolines from which a phosphine oxide is spontaneously eliminated.⁸⁵⁻⁸⁷ The ylids exist almost exclusively in the *cis*-enolate configuration, and a mechanism involving concerted 1,3-dipolar addition has been proposed (Scheme 12) on the basis that there is a low entropy of activation for the reaction, and that the reaction rate is insensitive to changes in solvent polarity.^{86, 87}



(R=H, alkyl, alkenyl; R¹=OEt, alkyl, aryl; R²=MeCO, EtOCO, Ts, Ar, PhCO)

SCHEME 12

With acyl and alkoxy carbonyl azides, 2*H*-triazoles are isolated, although the 1*H*-isomers are detected as intermediates.⁸⁷ The reaction is not very general; it fails with the corresponding sulfonium ylids,⁸⁸ and fairly minor changes in substituents on the phosphorus ylid result in the formation of diazoketones rather than triazoles.^{85, 86}

⁸⁵ G. R. Harvey, *J. Org. Chem.* **31**, 1587 (1966).

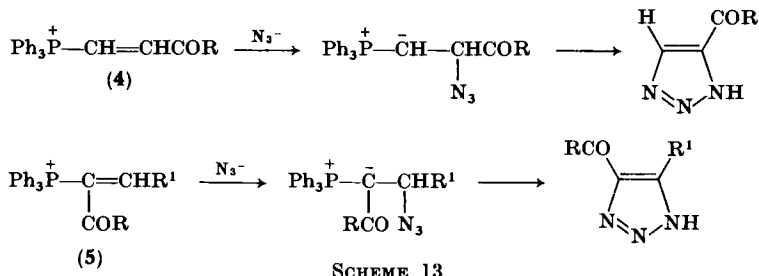
⁸⁶ G. L'abbé and H. J. Bestmann, *Tetrahedron Lett.*, 63 (1969); G. L'abbé, P. Ykman, and G. Smets, *Tetrahedron* **25**, 5421 (1969); **27**, 845 (1971); P. Ykman, G. Mathys, G. L'abbé, and G. Smets, *J. Org. Chem.* **37**, 3213 (1972).

⁸⁷ P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron* **27**, 5623 (1971).

⁸⁸ E. Van Loock, G. L'abbé, and G. Smets, *Tetrahedron Lett.*, 1693 (1970).

2. From Sodium Azide and Vinylphosphonium Salts

Phosphonium salts of the types 4 and 5 react with sodium azide in aqueous solution to give *v*-triazoles in high yield.⁸⁹ The proposed mechanism (Scheme 13) involves nucleophilic attack at the carbon β -to the phosphorus, followed by cyclization with displacement of triphenylphosphine.



SCHEME 13

3. From Azides and Enamines or Enol Ethers

Several azides are observed to undergo addition to enamines (Scheme 14)⁹⁰⁻⁹⁷ and to enol ethers.^{21, 97-100} The reaction conditions are mild: Typically, the reagents are heated together in chloroform for 1-2 hours.

⁸⁹ M. Rasberger and E. Zbiral, *Monatsh.*, **100**, 64 (1969); E. Zbiral and J. Strohs, *ibid.*, p. 1438; E. Zbiral, M. Rasberger, and H. Hengstberger, *Ann.* **725**, 22 (1969).

⁹⁰ R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 849 (1961); R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *ibid.* **92**, 1040 (1962); *Chem. Ber.* **96**, 802 (1963); G. Bianchetti, P. Dalla Croce, and D. Pocar, *ibid.*, **97**, 1225 (1964); *Rend. Ist. Lombardo Sci. Lettere A*, **99**, 259 (1965) [*Chem. Abstr.* **65**, 7173 (1966)]; D. Pocar, R. Stradi, and L. M. Rossi, *J. Chem. Soc., Perkin Trans. I*, 619, 769 (1972); Y. K. Kim and M. E. Munk, *J. Amer. Chem. Soc.* **86**, 2213 (1964); M. Regitz and G. Himbert, *Ann* **734**, 70 (1970).

⁹¹ G. Bianchetti, P. Dalla Croce, and D. Pocar, *Gazz. Chim. Ital.* **94**, 340 (1964).

⁹² P. N. Neuman, *J. Heterocycl. Chem.* **8**, 51 (1971).

⁹³ P. Ferruti, D. Pocar, and G. Bianchetti, *Gazz. Chim. Ital.* **97**, 109 (1967).

⁹⁴ D. Pocar, S. Maiorana, and P. Dalla Croce, *Gazz. Chim. Ital.* **98**, 949 (1968).

⁹⁵ G. Bianchetti, D. Pocar, P. Dalla Croce, and A. Vigevani, *Chem. Ber.* **98**, 2715 (1965).

⁹⁶ G. Bianchetti, P. Dalla Croce, D. Pocar, and A. Vigevani, *Gazz. Chim. Ital.* **97**, 289, 304 (1967).

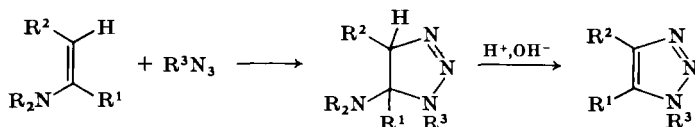
⁹⁷ G. Bianchetti, P. Ferruti, and D. Pocar, *Gazz. Chim. Ital.* **97**, 579, 597 (1967).

⁹⁸ A. Lionetti, R. Scarpatti, and D. Sica, *Gazz. Chim. Ital.* **93**, 90 (1963).

⁹⁹ R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.* **98**, 1138 (1965).

¹⁰⁰ R. Scarpatti, M. L. Graziano, and R. Nicolaus, *Gazz. Chim. Ital.* **99**, 1339 (1969).

The products are triazolines with the amino or alkoxy function in the 5-position: Addition is regiospecific. In some cases the triazolines aromatize spontaneously; more usually, aromatization is effected by heating the compounds alone (for enol ether adducts) or with acid or base.

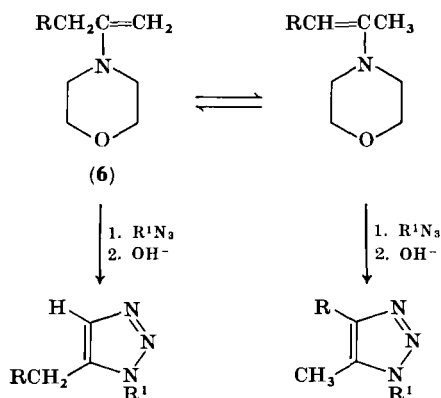


SCHEME 14

A competing reaction is thermal elimination of nitrogen from the triazolines. Some triazolines derived from cyclic enol ethers and enamines failed to give triazoles for this reason.⁹⁹ In general, however, yields are very good.

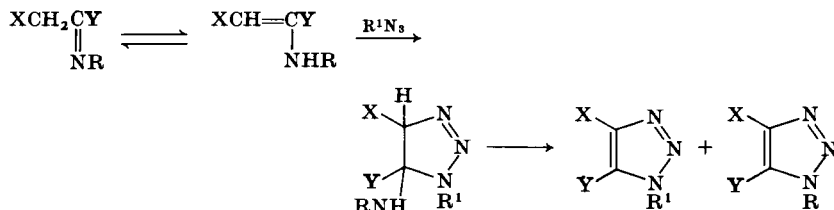
The reaction is most effective with azides bearing electron-withdrawing groups, such as nitrophenyl, toluene-*p*-sulfonyl, and ethoxycarbonyl. Sulfonyl azide adducts give *N*-unsubstituted triazoles, the substituent being lost on aromatization. The triazole which is isolated as a minor product of the reaction of 1,1-dimethoxyethylene with ethoxycarbonyl azide¹⁰⁰ has been assigned a 2*H*-triazole structure;⁵⁵ it is likely that other ethoxycarbonyltriazoles formed by this route also have 2*H*-structures.

Mixtures of triazoles are obtained from enamines in which tautomerism is possible. For example, addition is observed to both tautomers of enamines of the type 6 (Scheme 15).⁹⁵



SCHEME 15

Imines derived from ketones with an α -methylene group can react via their enamine tautomers, and mixtures of triazoles are also isolated from these systems.⁹⁶ The triazoline adducts of the enamine tautomers are aromatized by treating with acid, and in these conditions the triazoline appears to undergo a Dimroth rearrangement before elimination of the amine, because two triazoles are obtained, one of which has



SCHEME 16

the imine nitrogen in the ring (Scheme 16). An example of triazole formation from primary enamine has also been described.¹⁰¹

4. From Azides and Olefins with Electron-Withdrawing Substituents

Olefins, $\text{RCH}=\text{CHX}$, with a strongly electron-withdrawing substituent X (CN, NO_2 , Cl, F, SO_2Cl) react with organic azides to give triazolines of varying stability; from these a stable fragment can be eliminated to give triazoles. The addition of the azides is not regiospecific, and yields of triazoles are moderate.¹⁰²⁻¹⁰⁵

Sodium azide also adds to olefins of this type to give *v*-triazoles in fairly good yields.^{69, 104, 105} A mechanism involving nucleophilic displacement of the substituent X by azide, followed by cyclization of the vinyl azide in the presence of azide ions, has been suggested.¹⁰⁵ An alternative mechanism involves conjugate addition of azide to the double bond, cyclization of the resulting anion, and aromatization.

¹⁰¹ H. Warnhoff and P. Sohar, *Chem. Ber.* **104**, 3510 (1971).

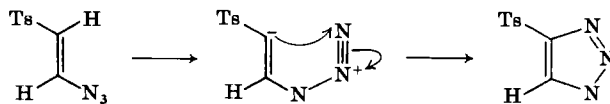
¹⁰² C. S. Rondestvedt and P. K. Chang, *J. Amer. Chem. Soc.* **77**, 6532 (1955).

¹⁰³ N. K. Kochetkov, *J. Gen. Chem. USSR* **25**, 1313 (1955); G. Rembarz, B. Kirchhoff, and G. Dongowski, *J. Prakt. Chem.* **33**, 199 (1966); W. R. Carpenter, A. Haymaker, and D. W. Moore, *J. Org. Chem.* **31**, 789 (1966).

¹⁰⁴ A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR* **167**, 109 (1966); *Chem. Abstr.* **64**, 17578 (1966); R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.* **99**, 475 (1966); Y. Tanaka and S. I. Miller, *J. Org. Chem.* **37**, 3370 (1972).

¹⁰⁵ P. D. Callaghan and M. S. Gibson, *Chem. Commun.*, 918 (1967); J. S. Meek and J. S. Fowler, *J. Org. Chem.* **33**, 985 (1968); N. S. Zefirov and N. K. Chapovskaya, *Zh. Org. Khim.* 1300 (1968); 2596 (1970); N. S. Zefirov, N. K. Chapovskaya, and V. V. Kolesnikov, *Chem. Commun.*, 1001 (1971).

An intramolecular counterpart of this reaction is the cyclization (Scheme 17) of anions derived from vinyl azides;^{49, 106} the neutral azides fail to cyclize,⁴⁹ presumably because the cyclic tautomer (the 4*H*-triazole) is not aromatic, whereas the anion is.



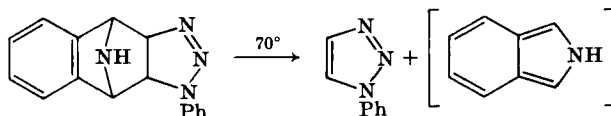
SCHEME 17

5. By Oxidation of Triazolines

Where the addition of an azide to an olefin shows greater regioselectivity than the addition to the corresponding acetylene, it may be convenient to obtain the triazole indirectly from the triazoline, by oxidation. Thus, addition of phenyl azide to acrylic and cinnamic esters gives the open-chain tautomers of the corresponding 4-alkoxy-carbonyltriazolines,^{104, 107} which are oxidized in good yield to the triazoles by permanganate. Addition of phenyl azide to quinones gives triazolines which are spontaneously oxidized to the triazoles.^{1, 2, 4}

6. By Retro-Diels–Alder Reactions of Triazolines

The energy gained in producing the aromatic triazole system facilitates the retro-Diels–Alder reaction of suitably substituted triazolines.^{108, 109} The reaction is potentially useful as a method of synthesis of highly reactive species (e.g., Scheme 18) rather than as a preparative procedure for triazoles.



SCHEME 18

7. From Azides and Allenes

An example of the reaction of an azide with an allene is known: the cycloaddition of phenyl azide to cyanoallene, which gives 4-cyano-5-methyl-1-phenyltriazole.¹¹⁰

¹⁰⁶ J. S. Meek and J. S. Fowler, *J. Amer. Chem. Soc.* **89**, 1967 (1967).

¹⁰⁷ F. Texier and R. Carrié, *Bull. Soc. Chim. Fr.*, 3642 (1971).

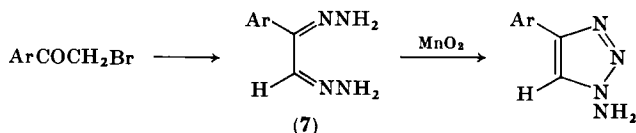
¹⁰⁸ G. Wittig and B. Reichel, *Chem. Ber.* **96**, 2851 (1963).

¹⁰⁹ K. Alder and W. Trimborn, *Ann.* **566**, 58 (1950).

¹¹⁰ W. Ried and H. Mengler, *Ann.* **678**, 95 (1964).

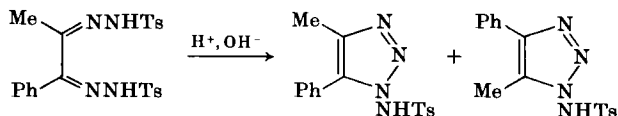
D. 1H-TRIAZOLES FROM α -DIKETONE DERIVATIVES

1-Aminotriazoles and their derivatives can be prepared from bis hydrazones and from substituted bis hydrazones of α -diketones. The bis hydrazones may in some cases be prepared more conveniently from α -bromoketones than from α -diketones.¹¹¹⁻¹¹³ Oxidation with mercuric oxide or with manganese dioxide gives the 1-aminotriazoles directly (Scheme 19).^{33, 111-113} Although two isomeric triazoles would be expected from unsymmetrical bis hydrazones, the bis hydrazones (7) gave only the 4-phenyltriazaoles. The mechanism has been elucidated by ¹⁵N-labeled experiments and the nature of the product confirmed by an X-ray structure determination.¹¹³



SCHEME 19

A disadvantage of this method of synthesis is that unless the conditions are carefully controlled, complete oxidation of the bis hydrazone occurs, the product being an acetylene. This problem can normally be avoided by using bis toluene-*p*-sulfonylhydrazones.¹¹⁴⁻¹¹⁶ These are



SCHEME 20

cyclized using either acid or base to give 1-toluenesulfonylamino-1H-triazoles, which can be converted into the 1-aminotriazoles in sulfuric acid (Scheme 20). In this reaction, derivatives of unsymmetrical diketones give both possible triazoles.¹¹⁶ Under certain conditions of base-catalyzed cyclization, acetylenes are also formed in this reaction.¹¹⁴

¹¹¹ S. Hauptmann, H. Wilde, and K. Moser, *Tetrahedron Lett.*, 3295 (1967).

¹¹² S. Hauptmann, H. Wilde, and K. Moser, *J. Prakt. Chem.* **313**, 882 (1971).

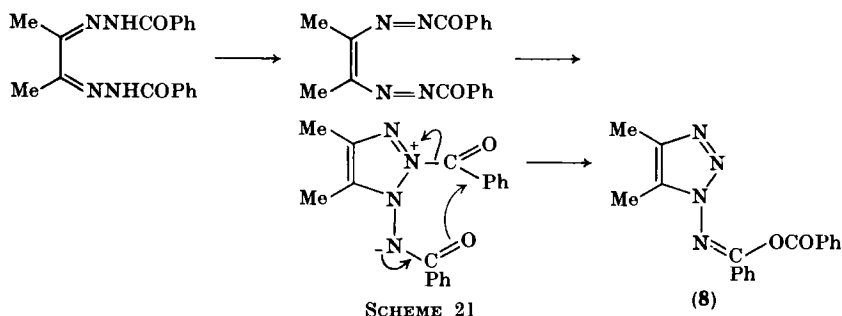
¹¹³ J. Sieler, H. Wilde, and S. Hauptmann, *Z. Chem.* **11**, 179 (1971).

¹¹⁴ W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

¹¹⁵ G. Wittig and H.-L. Dorsch, *Ann.* **711**, 46 (1968); G. Wittig and J. Meske-Schüller, *ibid.* **711**, 65 (1968).

¹¹⁶ T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 555 (1973).

Bis acylhydrazones or bis aroylhydrazones of α -diketones also give derivatives of 1-aminotriazoles on mild oxidation (Scheme 21).^{1, 117, 118} The product was originally assigned a dihydrotetrazine structure, and other possibilities were considered,¹¹⁷ but Curtin and Alexandrou proposed^{117, 118} the isoimide structure (8) which was, for the product obtained from biacetyl bis(benzoylhydrazone), confirmed by X-ray crystallography.¹¹⁸ The mechanism given in Scheme 21 has been put forward for its formation:



A bis-azoethylene derivative has been shown to cyclize to a 1-amino-triazole derivative on mild acid treatment.¹¹⁹

E. OTHER ROUTES TO 1H-TRIAZOLES

1. By Ring Closure of α -Diazoimines and α -Diazoamides

The ring closure of α -diazoimines (Scheme 22) is a well-established route to *v*-triazoles and to 1*H*-triazoles.² The α -diazoimines may be prepared *in situ* from α -diazoketones and amines,^{2, 120, 121} or by diazo transfer (Section II, B). A diazirine (the cyclic isomer of a diazoalkane) has also been used.¹²²

¹¹⁷ D. Y. Curtin and N. E. Alexandrou, *Tetrahedron* **19**, 1697 (1963); N. E. Alexandrou, *ibid.* **22**, 1309 (1966); S. Petersen and H. Heitzer, *Angew. Chem. Int. Ed. Engl.* **9**, 67 (1970).

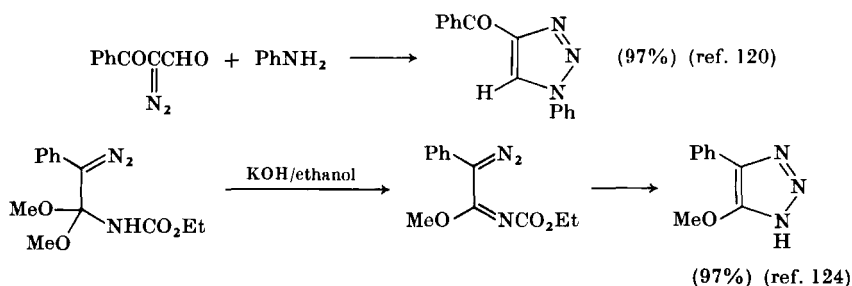
¹¹⁸ H. Bauer, A. J. Boulton, W. Fedeli, A. R. Katritzky, A. Majid-Hamid, F. Mazza, and A. Vaciago, *J. Chem. Soc., Perkin Trans. 2*, 662 (1972).

¹¹⁹ D. Y. Curtin, R. J. Crawford, and D. K. Wedegaertner, *J. Org. Chem.* **27**, 4300 (1962).

¹²⁰ F. M. Stojanovic and Z. Arnold, *Coll. Czech. Chem. Commun.* **32**, 2155 (1967).

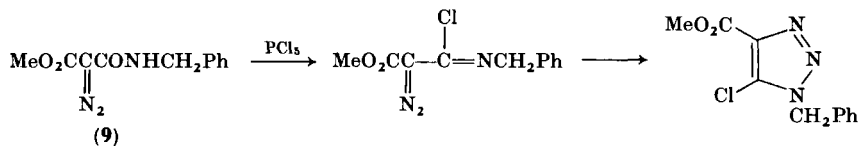
¹²¹ G. Desimoni and G. Minoli, *Tetrahedron* **26**, 1393 (1970); B. Eisert and E. Endres, *Ann.* **734**, 56 (1970).

¹²² E. Schmitz and C. Hoerig, *Chem. Ber.* **100**, 2101 (1967).



SCHEME 22

α -Diazoamides also give triazoles, on heating¹²³ or by treatment with base.¹²⁴ Reaction of the diazoamide (9) with phosphorus pentachloride gave a 5-chlorotriazole derivative through an intermediate imidoyl chloride (Scheme 23).¹²⁵



SCHEME 23

2. By Ring Closure of α -Aminodiazonium Salts

This synthetic method is widely used for benzotriazole derivatives but is of very limited use for monocyclic triazoles. 4,5-Dicyano-*v*-triazole has been prepared by this method. The method has also been applied to some α -aminoamides and amidines, but is not successful in every case.¹²⁶

3. From Diazoalkanes and Imines or Nitriles

v-Triazoles have been isolated from the reaction of several activated nitriles,^{3, 127} such as cyanogen, cyanogen halides, methyl cyanofornate, and cyanic acid esters,¹²⁸ with diazoalkanes. The reaction can formally be regarded as a 1,3-dipolar cycloaddition. The *v*-triazoles may be

¹²³ J. H. Looker and J. W. Carpenter, *Can. J. Chem.* **45**, 1727 (1967).

¹²⁴ M. Regitz and H. J. Geelhaar, *Chem. Ber.* **102**, 1743 (1969); R. Scarpati and M. L. Graziano, *Tetrahedron Lett.* 2085 (1971).

¹²⁵ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **21**, 633 (1967).

¹²⁶ A. H. Cook, I. Heilbron, and D. G. Hunter, *J. Chem. Soc.*, 1443 (1949); I. Tejima, Japanese Patent 4856 (1957) [*Chem. Abstr.* **52**, 5479f (1958)].

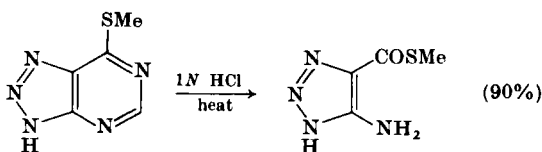
¹²⁷ B. L. Dyatkin, K. N. Makarov, and I. L. Knunyants, *Tetrahedron* **27**, 51 (1971).

¹²⁸ D. Martin and A. Weise, *Chem. Ber.* **99**, 317 (1966).

alkylated if an excess of the diazoalkane is used.^{129, 130} With less-activated nitriles, such as benzonitrile¹³⁰ and cuprous cyanide,¹³¹ aluminum alkyls have been used as catalysts. Diazomethylithium has also been added to benzonitrile;¹³² in this case the reaction probably involves nucleophilic attack on the nitrile. Reactions of diazoalkanes with certain oximes,¹³³ ketenimines,¹³⁴ and carbodiimides^{135, 136} are also reported to give 1*H*-triazoles, but these routes may not be capable of general application. Lithium salts of *N*-nitrosoalkylamines also give triazoles with aromatic nitriles.^{136a}

4. By Degradation of Fused Triazoles

Oxidation of benzotriazoles and other fused triazoles by potassium permanganate is a well-established route to 1*H*-triazole 4,5-dicarboxylic acid derivatives.^{2, 137} Many of the triazolo[*d*]pyrimidines, synthesized as purine analogs, can be degraded to monocyclic triazoles by acidic or basic hydrolysis¹³⁸⁻¹⁴⁰ (in other triazolopyrimidines, however, the triazole ring is cleaved preferentially⁷⁷), e.g. Scheme 24.

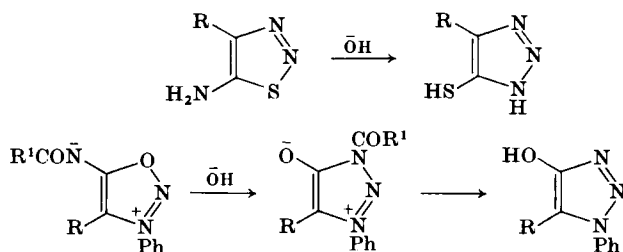


SCHEME 24

- ¹²⁹ J. M. Stewart, R. L. Clark, and P. E. Pike, *J. Chem. Eng. Data* **16**, 98 (1971); *Chem. Abstr.* **74**, 76377 (1971).
¹³⁰ H. Hoberg, *Ann* **707**, 147 (1967).
¹³¹ I. P. Lavrent'ev, L. G. Korableva, and M. L. Khidekel', *Bull. Acad. Sci. USSR*, 894 (1969).
¹³² E. Müller and D. Ludsteck, *Chem. Ber.* **88**, 921 (1955).
¹³³ H. J. Backer, *Rec. Trav. Chim.* **69**, 1223 (1950).
¹³⁴ M. W. Barker and J. H. Gardner, *J. Heterocycl. Chem.* **6**, 251 (1969).
¹³⁵ S. Hauptmann and K. Hirschberg, *J. Prakt. Chem.* **36**, 82 (1967).
¹³⁶ M. F. Lappert and J. S. Poland, *J. Chem. Soc. C*, 3910 (1971).
^{136a} D. Seebach and D. Enders, *Angew. Chem. Int. Ed. Engl.* **11**, 1102 (1972).
¹³⁷ H. Reimlinger, *Chem. Ber.* **97**, 3493 (1964); R. Huisgen and V. Weberndörfer, *ibid.* **100**, 71 (1967).
¹³⁸ S. Yamada and T. Mizoguchi, Japanese Patent 10,468 ('59) [*Chem. Abstr.* **54**, 18555c (1960)]; D. G. Farnum and P. Yates, *J. Amer. Chem. Soc.* **85**, 2967 (1963).
¹³⁹ G. B. Brown, H. W. Smith, and M. A. Stevens, *J. Amer. Chem. Soc.* **82**, 3189 (1960).
¹⁴⁰ A. Albert, *J. Chem. Soc. C*, 2379 (1969).

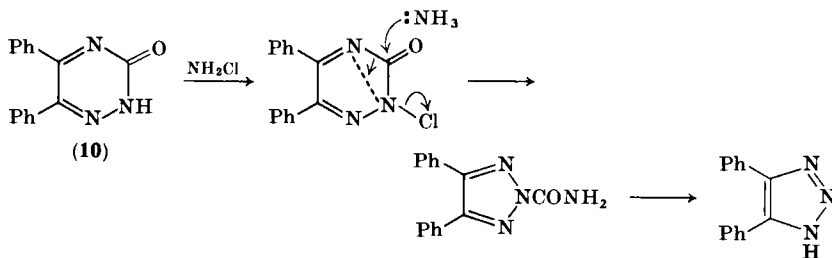
5. By Rearrangement or Degradation of Other Heterocyclic Systems

Examples of the Dimroth rearrangement (Section IV, F) include several syntheses of monocyclic triazoles from other heterocyclic systems (cf. Scheme 25). Triazole-5-thiols can be prepared by treatment of 5-amino-1,2,3-thiadiazoles with bases.¹⁴¹⁻¹⁴³ A similar base-induced rearrangement of sydnoneimines provides a synthesis of 4-hydroxy-triazoles.¹⁴⁴



SCHEME 25

Two types of reaction are known which involve ring contraction of six-membered heterocyclic systems and present mechanistically intriguing problems. One is the ring contraction of the diphenyltriazinone (10): Treatment with chloramine gives a 4,5-diphenyl-*v*-triazole in high yield. A mechanism (Scheme 26) involving a 2-carboxamidotriazole



SCHEME 26

intermediate has been suggested.¹⁴⁵ The 2-hydroxy derivative of the triazinone (10) also gives diphenyltriazole when heated in acetic anhydride.¹⁴⁶

¹⁴¹ T. Kindt-Larsen and C. Pedersen, *Acta Chem. Scand.* **16**, 1800 (1962).

¹⁴² J. G6rdeler and G. Gnad, *Chem. Ber.* **99**, 1618 (1966).

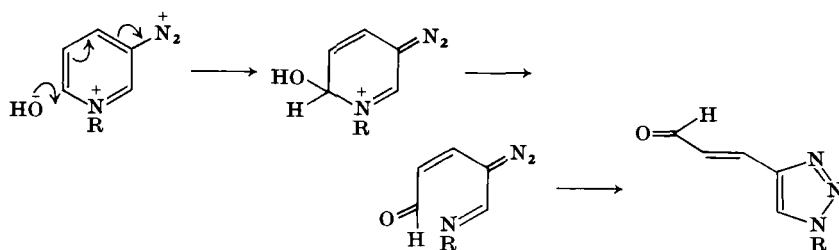
¹⁴³ M. Regitz and A. Liedhegener, *Ann* **710**, 118 (1967).

¹⁴⁴ H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2441 (1962).

¹⁴⁵ C. W. Rees and A. A. Sale, *J. Chem. Soc., Perkin Trans. 1*, 545 (1973).

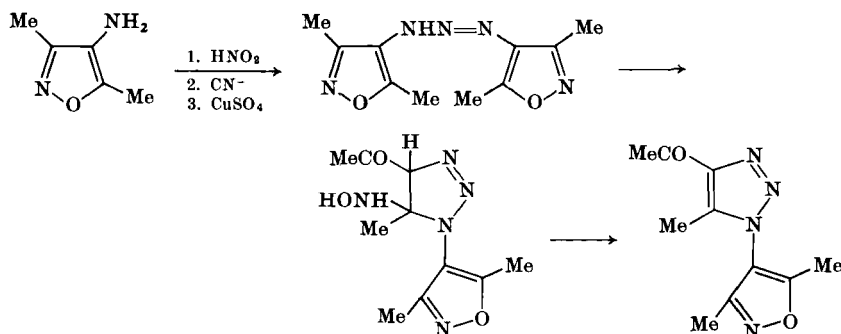
¹⁴⁶ T. Sasaki and K. Minamoto, *J. Org. Chem.* **31**, 3914 (1966).

The other ring contraction involves cleavage of the pyridine ring under very mild conditions. Diazotization of 3-aminopyridinium salts ($R = \text{alkyl, allyl, aryl}$) gives 1*H*-triazole-4-acraldehyde derivatives.¹⁴⁷ A possible mechanism for the reaction is shown in Scheme 27.



SCHEME 27

Diazotization of 4-amino-3,5-dimethylisoxazole also results in ring-opening and formation of a triazole (Scheme 28); a linear triazene is probably an intermediate.¹⁵¹



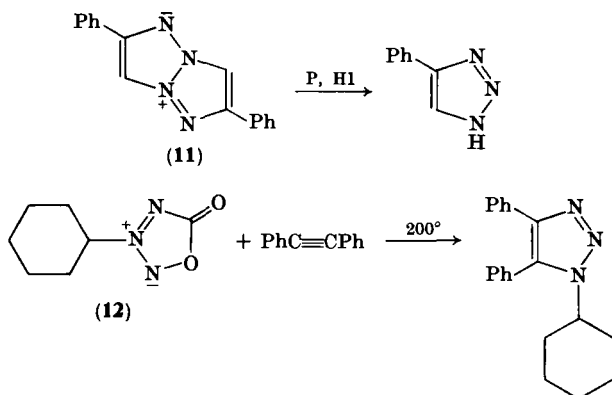
SCHEME 28

Other ring cleavages involve the reduction of the triazototriazole (**11**), which gives 4-phenyltriazole,¹⁴⁸ and the reaction of the mesoionic oxatriazolone (**12**) with diphenylacetylene, giving 1-cyclohexyl-4,5-diphenyltriazole, possibly through cyclohexyl azide as an intermediate

¹⁴⁷ W. König, M. Coenen, W. Lorenz, F. Bader, and A. Bassl, *J. Prakt. Chem.* **30**, 96 (1965); W. König, M. Coenen, F. Bahr, B. May, and A. Bassl, *ibid.* **33**, 54 (1966).

¹⁴⁸ R. Pflieger and H.-G. Hahn, *Chem. Ber.* **90**, 2411 (1957); R. Pflieger, E. Garthe, and K. Rauer, *ibid.* **96**, 1827 (1963).

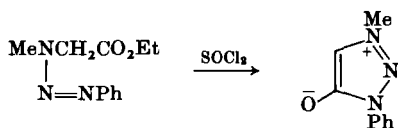
(Scheme 29).¹⁴⁹ The reaction of 5-aminotetrazole with diphenylacetylene may similarly involve the intermediacy of hydrazoic acid.¹⁵⁰



SCHEME 29

6. From Linear Triazenes

Linear triazenes are likely intermediates in some triazole syntheses^{151, 152} and have been employed as precursors of a few triazoles;^{153, 154} the reaction is useful for preparing mesoionic triazolium-5-oxides and -imines (see, e.g., Scheme 30).¹⁵⁴



SCHEME 30

F. 2H-TRIAZOLES FROM α -DIKETONE DERIVATIVES

1. By Oxidation of α -Diketone Bis Arylhydrazones

Oxidation of α -diketone bis arylhydrazones using a variety of reagents results in the formation of 2-aryl-1,2,3-triazoles. This reaction, which is

¹⁴⁹ R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.* **101**, 536 (1968).

¹⁵⁰ H. Reimlinger, *Chem. Ind. (London)*, 294 (1972).

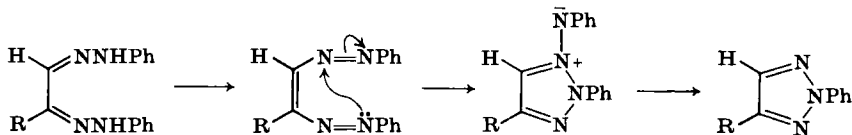
¹⁵¹ A. J. Boulton and A. R. Katritzky, *J. Chem. Soc.*, 2083 (1962).

¹⁵² R. Meier, *Chem. Ber.* **86**, 1483 (1953).

¹⁵³ P. A. S. Smith, G. J. W. Breen, M. K. Hajek, and D. V. C. Awang, *J. Org. Chem.* **35**, 2215 (1970).

¹⁵⁴ K. T. Potts and S. Husain, *J. Org. Chem.* **35**, 3451 (1970).

very general, has been used extensively for the preparation of sugar "osotriazoles" from osazones. The subject has been reviewed recently.¹⁵⁵ The sugar osotriazoles are readily degraded to simpler 2*H*-triazole derivatives so that their preparation leads to syntheses of a wide range of other 2*H*-triazoles. The nitrogen atom eliminated is the substituted nitrogen from the C-1 position for sugar osazones and for methylglyoxal.^{156, 157} Electron-withdrawing groups inhibit triazole formation,



SCHEME 31

and electron-releasing groups assist the reaction.¹⁵⁸ A bis(azo)-ethylene intermediate is probably involved; a possible mechanism for the reaction is shown in Scheme 31.^{158a}

Many oxidizing agents have been used, especially copper sulfate and other cupric salts.^{157, 159} Potassium dichromate in acetic acid¹⁶⁰ and manganese dioxide¹⁶¹ are good oxidants for benzil bis(phenylhydrazone). Nitrous acid has been used for the osazones of acetylated sugars¹⁶² and for phenylglyoxal bis(phenylhydrazone).¹⁶³

Examples have been described of cyclization of bis(azostilbene) derivatives by reaction with hydrogen sulfide and hydrochloric acid,¹⁶⁴ by irradiation,^{164a} and by heat.¹⁶⁵ 2,4,5-Triphenyltriazole is formed in each case. Nonoxidative cyclization of bis arylhydrazones is also reported.^{1, 166} A reaction related to these is the oxidation of benzaldehyde

¹⁵⁵ H. El Khadem, *Advan. Carbohydr. Chem. Biochem.* **25**, 351 (1970).

¹⁵⁶ G. Henseke and M. Winter, *Chem. Ber.* **93**, 45 (1960); L. Mester and F. Weygand, *Bull. Soc. Chim. Fr.*, 350 (1960); L. Mester, *ibid.* 381 (1962).

¹⁵⁷ G. Henseke and G. Müller, *J. Prakt. Chem.* **18**, 47 (1962).

¹⁵⁸ H. El Khadem, Z. M. El-Shafei, and M. H. Meshreki, *J. Chem. Soc.*, 2957 (1961).

^{158a} Evidence relating to this mechanism is presented by K. B. Sukumaran, C. S. Angadiyavar, and M. V. George, *Tetrahedron* **28**, 3987 (1972).

¹⁵⁹ H. El Khadem and Z. M. El-Shafei, *J. Chem. Soc.*, 3117 (1958).

¹⁶⁰ H. El Khadem, Z. M. El-Shafei, and M. M. Hashem, *J. Chem. Soc. C*, 949 (1968).

¹⁶¹ I. Bhatnagar and M. V. George, *J. Org. Chem.* **32**, 2252 (1967).

¹⁶² H. El Khadem, M. M. El-Sadik, and M. H. Meshreki, *J. Chem. Soc. C*, 2097 (1968).

¹⁶³ H. Alfes, H. El Khadem, and M. L. Wolfram, *J. Org. Chem.* **29**, 2072 (1964).

¹⁶⁴ A. Spasov and B. Chemishev, *Dokl. Bolg. Akad. Nauk.* **23**, 791 (1970) [*Chem. Abstr.* **73**, 120593 (1970)].

^{164a} C. Wintner, *Tetrahedron Lett.*, 2275 (1971).

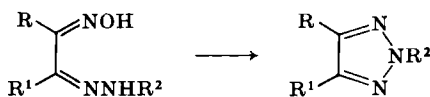
¹⁶⁵ C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971).

¹⁶⁶ J. H. Boyer and L. R. Morgan, *J. Amer. Chem. Soc.* **80**, 3012 (1958).

phenylhydrazone with manganese dioxide, which also gives triphenyl-triazole, probably through benzil bis(phenyl)hydrazone as an intermediate.¹⁶¹

2. By Dehydration of α -Diketone Hydrazone Oximes

Another general method of synthesis of 2H-triazoles involves intramolecular elimination of water from adjacent hydrazone and oxime functions (Scheme 32). The usual reagent is acetic anhydride,¹⁶⁷⁻¹⁶⁹ but others, including phosphorus pentachloride¹⁷⁰ and urea,¹⁷¹ have been used.



SCHEME 32

If the hydrazone is unsubstituted, dehydration with acetic anhydride gives a 2-acetyltriazole, which is readily converted into an unsubstituted *v*-triazole.¹⁶⁷ Oxidation of α -diketone hydrazone oximes with cupric sulfate in aqueous pyridine leads to the formation of 2H-triazole-1-oxides.¹⁷²

3. By Oxidation of α -Diketone Hydrazone Imines

Oxidation of α -diketone hydrazone imines with cuprammonium salts gives 2H-triazoles.¹⁷³ With substituted imines (using *N*-bromosuccinimide as oxidant) 1,2-disubstituted triazolium salts are obtained (Scheme 33).¹⁷⁴

¹⁶⁷ M. Ruccia, *Ann. Chim.* **50**, 1363 (1960).

¹⁶⁸ R. Mohr and M. Zimmerman, German Patent 1,168,437 [*Chem. Abstr.* **61**, 1873 (1964)]; E. J. Browne, *Aust. J. Chem.* **22**, 2251 (1969); K. Weber, P. Liechti, H. R. Meyer, and A. E. Siegrist, Swiss Patent 485014 [*Chem. Abstr.* **72**, 134456 (1970)].

¹⁶⁹ A. Dorlars and W. D. Wirth, S. African Patent 6,808,154 [*Chem. Abstr.* **72**, 112806 (1970)].

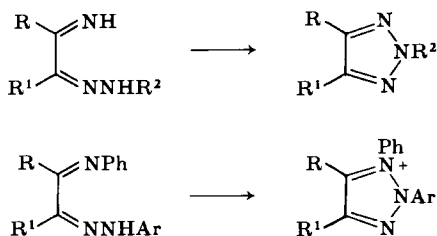
¹⁷⁰ P. Catsoulakus, *Chem. Chron. A*, **33**, 13 (1968) [*Chem. Abstr.* **69**, 77582 (1968)].

¹⁷¹ Farbenfabriken Bayer A.-G., French Patent 1,577,760 [*Chem. Abstr.* **72**, 100716 (1970)].

¹⁷² J. R. Geigy A.-G., French Patent 1,556,529 [*Chem. Abstr.* **72**, 122925 (1970)].

¹⁷³ E. Richter and E. C. Taylor, *J. Amer. Chem. Soc.* **78**, 5848 (1956); F. Muzik and M. Vesely, Czechoslovak Patent 99096 [*Chem. Abstr.* **57**, 16800 (1962)]; J. Cuipe and B. Hirsch, *Chimia* **17**, 159 (1963); B. Hirsch, German Patent 1,226,591 [*Chem. Abstr.* **66**, 28775 (1967)]; M. Vesely, F. Muzik, and J. Poskočil, *Coll. Czech. Chem. Commun.* **26**, 2530 (1961); O. Neuner, A. Dorlars, C. W. Schellhammer, and O. Berendes, British Patent 1,113,918 [*Chem. Abstr.* **69**, 52937 (1968)]; Farbenfabriken Bayer A.-G., French Patent 1,508,550 [*Chem. Abstr.* **70**, 38909 (1969)].

¹⁷⁴ E. Förster and B. Hirsch, *Naturwissenschaften* **50**, 374 (1963).

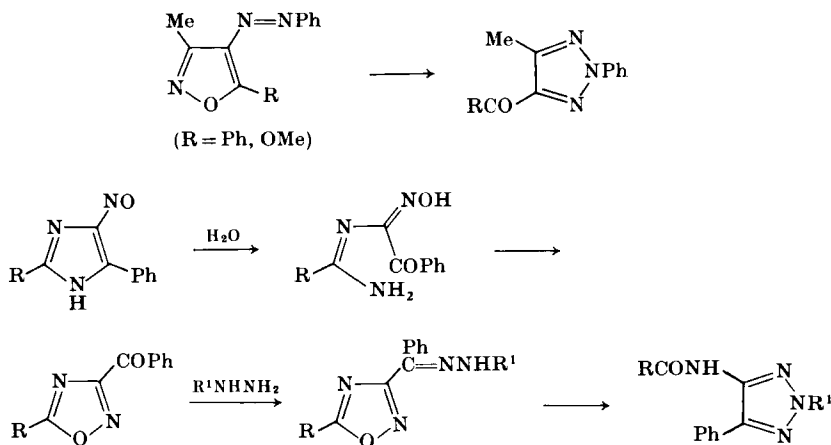


SCHEME 33

G. OTHER ROUTES TO 2H-TRIAZOLES

1. From Other Heterocyclic Systems

4-Arylazoisoxazoles can rearrange to 2-aryltriazoles,¹⁷⁵ and 4-amino-2H-triazoles can be prepared by reaction of 4-nitrosoimidazoles with hydrazines (Scheme 34). The hydrazones of 3-benzoyloxadiazoles are intermediates in the latter reaction.¹⁷⁶ The generality of rearrangements of this type has been discussed, and a further example, involving the rearrangement of a 1,2,5-oxadiazole to a triazole, has been described.^{176a}



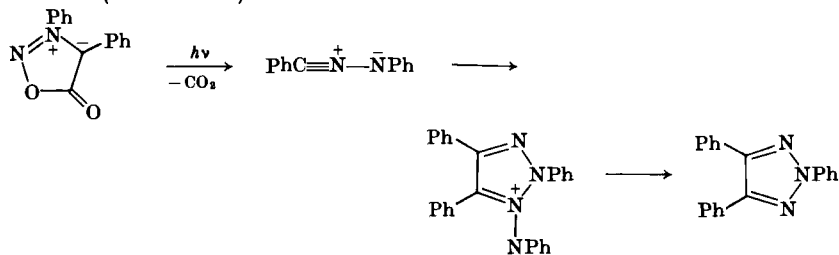
SCHEME 34

¹⁷⁵ P. F. H. Freeman, D. J. Shields, and L. A. Summers, *J. Chem. Soc.*, 3312 (1965).

¹⁷⁶ M. Ruccia and D. Spinelli, *Gazz. Chim. Ital.* **89**, 1654 (1959); S. Cusmano, G. Natale, and M. Ruccia, *ibid.* **90**, 831 (1960); G. Natale and M. Ruccia, *ibid.* **90**, 1047 (1960); M. Ruccia and G. Werber, *ibid.* **90**, 1140 (1960).

^{176a} A. J. Boulton, A. R. Katritzky, and A. Majid Hamid, *J. Chem. Soc. C*, 2005 (1967).

Photolysis of 3,4-diphenylsydnone gives 2,4,5-triphenyltriazole as a major product; a nitrilimine is believed to be an intermediate in this reaction (Scheme 35).¹⁷⁷

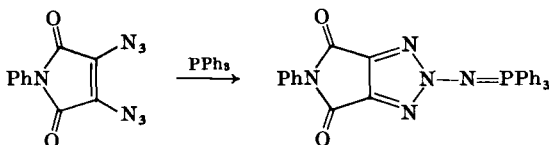


SCHEME 35

Photolysis of 2-methyl-5-phenyltetrazole gives 4,5-diphenyl-2-methyltriazole. This may also be formed through a nitrilimine intermediate, although the mechanism has not been established.¹⁷⁸

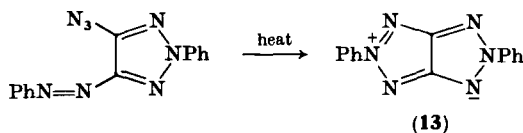
2. From Azides

Very few 2*H*-triazole syntheses involve azides, apart from those (such as 2-acetyl derivatives) which involve prior formation and rearrangement of 1*H*-triazoles. Some vinyl diazides react with triphenylphosphine in mild conditions to give iminophosphoranes of 2-amino-triazoles (Scheme 36).¹⁷⁹



SCHEME 36

The triazolotriazole (13) has been prepared by cyclization of an azido derivative (Scheme 37).¹⁸⁰



SCHEME 37

¹⁷⁷ C. S. Angadiyavar and M. V. George, *J. Org. Chem.* **36**, 1589 (1971); M. Märky, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 1275 (1971); Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jap.* **44**, 1667 (1971).

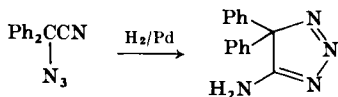
¹⁷⁸ R. R. Fraser, Gurudata, and K. E. Haque, *J. Org. Chem.* **34**, 4118 (1969).

¹⁷⁹ W. L. Mosby and M. L. Silva, *J. Chem. Soc.*, 1003 (1965).

¹⁸⁰ L. A. Henderson, U.S. Patent 3,541,107 [*Chem. Abstr.* **74**, 65596 (1971)]; see also M. Yoshida, A. Matsumoto, and O. Simamura, *Bull. Chem. Soc. Jap.* **43**, 3587 (1970).

H. 4*H*-TRIAZOLES

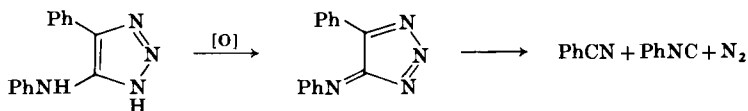
5-Amino- and 5-hydroxy-4*H*-triazoles have been reported as products



SCHEME 38

of the reduction of α -azidonitriles and esters (e.g., Scheme 38).³

Oxidation of 5-anilino-4-phenyl-*v*-triazole may give a 4*H*-triazolone derivative as an intermediate (Scheme 39).^{181, 182}



SCHEME 39

Otherwise, 4*H*-triazole derivatives apparently exist in their open-chain tautomeric forms, as vinyl azides (see Scheme 40). It remains to be shown whether vinyl azides and the isomeric 4*H*-triazoles can have independent existence; attempts to cyclize vinyl azides have not been successful.⁴⁹



SCHEME 40

III. Structure and Physical Properties

A. STRUCTURE

v-Triazole appears to contain both 1*H*- and 2*H*-tautomers at equilibrium in dilute solution.¹⁸³ In more concentrated solution the molecules

¹⁸¹ P. A. S. Smith, L. O. Krbecek, and W. Resemann, *J. Amer. Chem. Soc.* **86**, 2025 (1964).

¹⁸² E. M. Burgess and J. P. Sanchez, *J. Org. Chem.* **38**, 176 (1973) describe a similar intermediate.

¹⁸³ M. L. Roumestant, P. Viallefont, J. Elguero, R. Jacquier, and E. Arnal, *Tetrahedron Lett.*, 495 (1969).

are associated, with the hydrogen atoms linking 1*H*-forms of the triazole;^{41, 184} the 1*H*-structure is also apparently favored in the vapor phase.¹⁸⁴

Several types of molecular orbital calculation have been carried out on the 1*H*- and the 2*H*-structures of *v*-triazole, and on simple alkyl derivatives;¹⁸⁵⁻¹⁹¹ from these, estimates of several physical properties, including bond lengths, resonance energy, electron densities, and dipole moments have been made. From the calculations it appears that the 2*H*-structure is slightly more stable than the 1*H*-form.¹⁸⁵

B. SPECTROSCOPIC PROPERTIES

1. Ultraviolet Spectra

1,2,3-Triazole absorbs at 210 nm (ethanol; log ϵ 3.64), as does the conjugate acid.¹⁹² Bathochromic shifts are observed for 4-alkyl derivatives (216 nm; log ϵ 3.65),¹⁹³ 4,5-dialkyl derivatives (228 nm; log ϵ 3.58),¹⁹⁴ the 4-amino derivative (239 nm; log ϵ 3.69),⁷⁰ and the 4-formamido derivative (224 nm; log ϵ 3.96).¹⁹⁵ The bathochromic shift in 4-amino-triazole and in 5-amino-1-methyltriazole¹⁴⁰ does not disappear in the protonated species, indicating that the amino group is not the site of protonation.

The 1- and 2-aryltriazoles are distinguishable by their ultraviolet spectra, the absorption maxima of the 2-substituted derivatives being

¹⁸⁴ E. Borello and A. Zecchina, *Ann. Chim. (Rome)* **52**, 1302 (1962); E. Borello, A. Zecchina, and E. Guglielminotti, *J. Chem. Soc. B*, 307 (1969); O. L. Stiefvater, H. Jones, and J. Sheridan, *Spectrochim. Acta Part A* **26**, 825 (1970).

¹⁸⁵ M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.* **44**, 759 (1966); M. Roche and L. Pujol, *Bull. Soc. Chim. Fr.*, 1097 (1969).

¹⁸⁶ J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2998 (1967).

¹⁸⁷ B. M. Lynch, *Chem. Commun.*, 1337 (1968).

¹⁸⁸ F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.* **90**, 3543 (1968).

¹⁸⁹ M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron* **28**, 637 (1972).

¹⁹⁰ W. Adam and A. Grimson, *Theor. Chim. Acta* **7**, 342 (1967).

¹⁹¹ S. Basu, *Proc. Nat. Inst. Sci. India, Part A* **21**, 173 (1955) [*Chem. Abstr.* **50**, 6175h (1956)]; W. Woznicki and B. Zurawski, *Acta Phys. Pol.* **31**, 95 (1967) [*Chem. Abstr.* **67**, 96327 (1967)]; J. D. Vaughan and M. O'Donnell, *Tetrahedron Lett.*, 3727 (1968); M. Roche and L. Pujol, *Bull. Soc. Chim. Fr.*, 273 (1970); M. Kamiya, *Bull. Chem. Soc. Jap.* **43**, 3344 (1970).

¹⁹² D. Dal Monte Casoni, A. Mangini, R. Passerini, and C. Zavli, *Gazz. Chim. Ital.* **88**, 977, 1035 (1958).

¹⁹³ L. W. Hartzel and F. R. Benson, *J. Amer. Chem. Soc.* **76**, 667 (1954).

¹⁹⁴ H. Rapoport and W. Nilsson, *J. Amer. Chem. Soc.* **83**, 4262 (1961).

¹⁹⁵ A. Albert, *J. Chem. Soc. C*, 2076 (1968).

at longer wavelengths. Thus 2-phenyltriazole absorbs at 262 nm ($\log \epsilon$ 4.21)¹⁹² compared with 244 nm ($\log \epsilon$ 4.26) for 1-phenyltriazole.⁸⁴ 4-Phenyltriazole absorbs at 247 nm ($\log \epsilon$ 4.06), the maximum being close to that of biphenyl.¹¹² The spectra of 1- and 2-alkyltriazoles are not sufficiently different to allow firm structural assignments.

The ultraviolet spectra may be of use in determining the position of further substitution of 1-aryltriazoles:^{84, 102} 4-Substituents produce a bathochromic shift whereas 5-substituents, probably for steric reasons, have the opposite effect. Thus 5-methyl-1-phenyltriazole absorbs at 230 nm ($\log \epsilon$ 3.84),⁸⁴ and the hindered 5-benzhydryl-1-*p*-bromophenyltriazole has an absorption maximum at 210 nm ($\log \epsilon$ 5.60).¹³⁴

Other structural applications of ultraviolet spectra include the detection of the open-chain tautomers of 1-cyanotriazoles⁵³ and assignments of structure to the isomers formed by Dimroth rearrangement of 1-anilinothiazoles.¹⁹⁶

The origin of the absorption bands in 1- and 2-substituted triazoles has been discussed.¹⁹²

2. Infrared Spectra

The spectrum of 1,2,3-triazole has been recorded in solution and in the vapor phase, and an analysis made of the absorption bands.¹⁸⁴ The conclusion is drawn that the asymmetric (1*H*-) structure is present in the vapor phase and in dilute solution (although a criticism of this interpretation has appeared¹⁹⁷). A similar conclusion is reached concerning the structure of 4-phenoxytriazole.¹²⁸

The NH stretching band in triazole appears in the vapor phase at 3522 cm⁻¹ and in carbon tetrachloride at 3470 cm⁻¹;¹⁸⁴ in the solid phase the NH absorption is a broad band at 2400–3300 cm⁻¹ (for 4-phenyltriazole).⁶ The CH stretching frequency of 4- or 5-unsubstituted triazoles is at 3100–3140 cm⁻¹ (liquid phase).⁷⁵ In-plane and out-of-plane deformation bands of the CH bond have also been distinguished at 1237 and 1076 cm⁻¹ (in the solution spectrum of 1,2,3-triazole),¹⁸⁴ at 1290–1150 and 850–700 cm⁻¹ (for various substituted triazoles)¹⁹⁸ and at 1149–1074 and 855–825 cm⁻¹ (for 2-aryltriazoles).¹⁹⁹

Many triazoles have been reported to have strong absorption bands in the region 1150–900 cm⁻¹, which may be due to ring breathing vibrations.

¹⁹⁶ E. Lieber, C. N. R. Rao, and T. S. Chao, *Spectrochim. Acta* **10**, 250 (1958).

¹⁹⁷ U. Croatto and A. Fava, *Ann. Chim. (Rome)* **54**, 735 (1964) [*Chem. Abstr.* **62**, 11197h (1965)].

¹⁹⁸ C. N. R. Rao and R. Venkataraghavan, *Can. J. Chem.* **42**, 43 (1964).

¹⁹⁹ E. Borello and A. Zecchina, *Spectrochim. Acta* **19**, 1703 (1963).

Other characteristic absorptions have been observed at 935–890 cm^{-1} in the spectra of *C*-benzoyltriazoles,²⁰⁰ and at 1640 cm^{-1} for triazolium oxides.⁷⁹ A comparison of the spectra of 1- and 2-propyltriazole shows that the latter spectrum contains fewer bands, because of the greater symmetry of the molecule.⁴¹

3. Nuclear Magnetic Resonance Spectra

The proton NMR spectrum of 1,2,3-triazole has been measured in several solvents.²⁰¹ The hydrogen atoms at C-4 and C-5 appear as a singlet at τ 2.10 (deuteriochloroform) which shifts to τ 2.04 in the anion, and to τ 1.31 in the protonated species (trifluoroacetic acid).^{201a} In other solvents values range from τ 1.90 (deuteriopyridine) to τ 2.58 (benzene). The NH proton appears at τ –5.9 (in deuteriochloroform).⁴¹ In deuterioacetone, the spectrum shows a temperature dependence and provides evidence for the existence of both the 1*H*- and the 2*H*-tautomers in solution at low temperature.¹⁸³ At 23°, the spectrum shows two small doublets at τ 1.88 and 2.30 besides the major singlet at τ 2.17. At –90° these peaks have shifted and their intensities have changed so that the two doublets appear at τ 1.68 and 2.17 and the singlet at τ 1.98, the intensities being approximately equal. The change is ascribed to a reversible solvation of the triazole which prevents the rapid exchange of protons within aggregates of triazole molecules.

The high-resolution ¹³C spectrum has also been measured, and the following values obtained:¹⁸⁸ chemical shift (in acetone) 62.4 ppm upfield from CS₂ (130.9 ppm downfield from tetramethylsilane); *J* (geminal) CH, 205 Hz; *J* (vicinal) CH, 13.4 Hz. The chemical shift value is in accord with an empirical equation based on the number and position of the nitrogen atoms in several five-membered heterocyclics, and also reflects the π -electron density of the system as calculated by the extended Hückel method^{188, 190} and by the simple MO method.¹⁸⁷ ¹⁴N spectra of *v*-triazole and of its 1- and 2-methyl derivative have also been obtained.¹⁸⁹

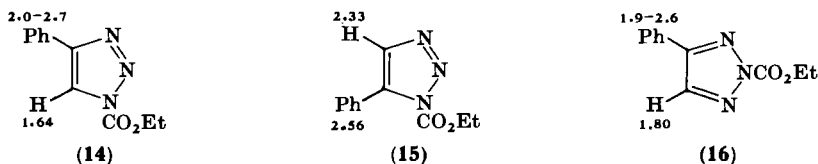
In substituted triazoles the positions of the signals due to triazole CH protons lie in the range 1.4–3.0 (in deuteriochloroform). Some trends are apparent in the chemical shift values. 1-Methyl or 2-methyl substitution moves the chemical shifts to slightly higher field; the hydrogen at C-5 of 1-methyltriazole appears at higher field than that at C-4.^{186, 201} An adjacent aroyl or ethoxycarbonyl substituent lowers the chemical

²⁰⁰ D. G. Farnum and P. Yates, *J. Org. Chem.* **27**, 2209 (1962).

²⁰¹ G. B. Barlin and T. J. Batterham, *J. Chem. Soc. B*, 516 (1967).

^{201a} Slightly different values are given in Elguero *et al.*¹⁸⁶

shift value, however.^{6, 87} This is useful, for example, in determining the structures of isomeric triazoles (Scheme 41).⁸⁷



SCHEME 41

Another important feature of these spectra is the type of signal given by the hydrogens of the phenyl group. The signal in the 5-phenyl-1*H*-isomer (15) is a singlet. This is ascribed to a steric interaction with the neighboring substituent, which causes the benzene ring to be twisted out of the plane of the triazole ring.⁸⁷ In the isomers 14 and 16 the benzene and triazole rings can be coplanar, so that the ortho hydrogens of the phenyl group are moved downfield by the electron-withdrawing triazole nucleus. The assignment of the 5-phenyl structure to 1*H*-triazoles which show a singlet for the phenyl hydrogens has been made in several instances.^{11, 12, 38, 87, 116} It does not appear to be an entirely general phenomenon, however,³⁸ and structural assignments made solely on this basis must be regarded as tentative.

NMR has also been used as a basis for distinguishing 1- and 2-acetyl-triazoles^{55, 76, 202} and for investigating ring-chain tautomerism in triazoles.^{15, 53, 203} ¹³C-H coupling constants are a useful means of determining the site of methylation of triazolo oxides, and triazolo sulfides.^{79, 204}

4. Mass Spectra

Several 1*H*-triazoles have been observed to undergo a primary loss of nitrogen ($M - 28$) in the mass spectrum.^{205, 206} The isomeric 2*H*-triazoles do not undergo this fragmentation,²⁰⁶ and this appears to provide a simple means of distinguishing 1*H*- and 2*H*-isomers. However, *v*-triazole can eliminate nitrogen from both the 1*H*- and the 2*H*-tautomer.^{206a}

²⁰² L. Birkofer and P. Wegner, *Chem. Ber.* **100**, 3485 (1967).

²⁰³ R. E. Harmon, F. Stanley, S. K. Gupta, R. A. Earl, J. Johnson, and G. Slomp, *Chem. Ind. (London)*, 1021 (1970).

²⁰⁴ M. Begtrup, *Acta Chem. Scand.* **25**, 3500 (1971).

²⁰⁵ N. E. Alexandrou and E. D. Micromastoras, *Tetrahedron Lett.*, 231 (1968); F. Compennolle and M. Dekeirel, *Org. Mass Spectrom.* **5**, 427 (1971).

²⁰⁶ T. L. Gilchrist, G. E. Gymer, and C. W. Rees, unpublished observations.

^{206a} A. Maquestiau, Y. Van Haverbeke, R. Flammang, and J. Elguero, *Org. Mass Spectrom.* **7**, 271 (1973).

C. OTHER PHYSICAL PROPERTIES

1. *Ionization Constants*

v-Triazole is a weak base (pK_a 1.17).²⁰⁷ 1-Methyltriazole is of comparable basicity (pK_a 1.25), but 2-methyltriazole is a much weaker base ($pK_a < 1$).²⁰⁷ Several aminotriazoles of which the pK_a 's are known are also weak bases;^{140, 195} for example, 5-amino-1-phenyltriazole has a pK_a of 2.27.¹⁴⁰

v-Triazole is also a weak acid (pK_a 9.42²⁰⁷; 9.26 ± 0.02 ²⁰⁸) of comparable strength to phenol. This NH ionization constant is not greatly affected by the presence of one or two carboxylic acid groups in the molecule, but 4,5-dibromotriazole is a much stronger acid (pK_a 5.37).²⁰⁸ These substituents have an unusual and unexplained effect on the thermodynamics of proton ionization from the triazole ring.²⁰⁸ 4-Nitrotriazole has a pK_a of 4.80,²⁰⁹ and triazoles with a carbonyl-containing function in the 4-position have pK_a values in the range 6.2–6.5.¹⁰⁴ The relative acidities of several triazolecarboxylic acids have been determined.^{84, 210}

A correlation has been noted between the pK_a values of several triazoles and their catalytic effect on the rate of hydrolysis of *p*-nitrophenyl acetate.²¹¹

2. *Dipole Moments*

The dipole moments of 1,4,5- and 2,4,5-triphenyltriazole have been determined as 5.2 and 0.4 μ respectively. The lower dipole moment of the 2*H*-isomer is used as a basis of structure assignment for 2,4,5-tris(trimethylsilyl)triazole, 0.94 μ .²⁷

3. *Optical Rotation*

In sugar osotriazoles, the phenylosotriazole chromophore is optically anisotropic. If the hydroxyl group at C-3 of a sugar is on the right in the Fischer projection, the derived osotriazole is dextrorotatory and gives a positive Cotton effect at 265 nm. Osotriazoles can thus be used for configurational assignment in sugars.²¹²

²⁰⁷ A. Albert, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), p. 98. Academic Press, New York, 1963.

²⁰⁸ L. D. Hansen, B. D. West, E. J. Baca, and C. L. Blank, *J. Amer. Chem. Soc.* **90**, 6588 (1968).

²⁰⁹ S. Maiorana, D. Pocar, and P. Dalla Croce, *Tetrahedron Lett.*, 6043 (1966).

²¹⁰ H. El Khadem, *J. Chem. Soc.*, 3146 (1961).

²¹¹ C. G. Overberger and P. S. Yuen, *J. Amer. Chem. Soc.* **92**, 1667 (1970).

²¹² H. El Khadem, *J. Org. Chem.* **28**, 2478 (1963); J. A. Mills, *Aust. J. Chem.* **17**, 277 (1964); G. Lyle and M. J. Piazza, *J. Org. Chem.* **33**, 2478 (1968).

IV. Reactions of 1,2,3-Triazoles

A. ELECTROPHILIC SUBSTITUTION

1. Alkylation

v-Triazoles and 1*H*-triazoles are readily alkylated on nitrogen by alkyl halides, dimethyl sulfate, diazomethane, and methyl toluene-*p*-sulfonate. Triazoles have also been alkylated by conjugate addition to activated olefins,^{41, 102, 213} by the Mannich reaction,²¹⁴ by condensation with an *O*-acetyl sugar derivative,^{214a} and by addition to aziridines.⁴¹ 4,5-Disubstituted *v*-triazoles in which the 4- and 5-substituents are different have been found to give all of the three possible monomethyl derivatives;^{206, 215} both possible methylation products are also obtained from symmetrically substituted triazoles such as 4,5-dibromo-^{213, 216} and 4,5-diphenyl-*v*-triazole,²⁰⁶ and from *v*-triazole itself.⁴¹ There appears to be some selectivity for 1-substitution when *v*-triazoles are methylated by the action of methyl iodide on the silver or thallium salts; on the other hand, methylation by the action of diazomethane on the neutral triazoles gives mainly the 2*H*-isomers.²⁰⁶ There is also some steric control. For example, 4-phenyltriazole gives with dimethyl sulfate the 2-methyl isomer (38%) and the 1-methyl-4-phenyl isomer (62%) but none of the more-hindered 1-methyl-5-phenyltriazole.¹³⁰ Alkylation of 4,5-diphenyltriazole by isopropyl iodide gives mainly the 2*H*-isomer, even with the silver salt.²⁰⁶

With N-1-substituted 1*H*-triazoles, 1,3-disubstituted triazolium salts are formed. 5-Hydroxy-1-alkyltriazoles are alkylated on oxygen, on N-2, and on N-3.^{79, 125} 2-Substituted 2*H*-triazoles are much more difficult to alkylate, but methyl fluorosulfonate has been used successfully: The products are 1,2-disubstituted triazolium salts.²¹⁷

C-Methylation of 1-phenyl-1*H*-triazoles has been achieved by their reaction with butyllithium and methyl iodide at low temperatures.²¹⁸

²¹³ D. Johnson, J. Moffat, N. Smith, and R. Wiley, *J. Amer. Chem. Soc.* **76**, 4933 (1954); J. E. Oliver and J. B. Stokes, *J. Heterocycl. Chem.* **7**, 961 (1970).

²¹⁴ J. J. Licari, L. W. Hartzel, G. Dougherty, and F. R. Benson, *J. Amer. Chem. Soc.* **77**, 5386 (1955).

^{214a} F. A. Lehmkuhl, J. T. Witkowski, and R. K. Robins, *J. Heterocycl. Chem.* **9**, 1195 (1972).

²¹⁵ A. Albert, *Angew. Chem. Int. Ed. Engl.* **8**, 132 (1969).

²¹⁶ M. Begtrup and P. A. Kristensen, *Acta Chem. Scand.* **23**, 2733 (1969).

²¹⁷ M. Begtrup and K. V. Poulsen, *Acta Chem. Scand.* **25**, 2087 (1971).

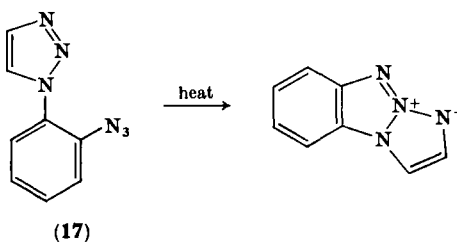
²¹⁸ R. Raap, *Can. J. Chem.* **49**, 1792 (1971).

2. Arylation

v-Triazole¹⁸⁶ and its 4-amino derivative²¹⁹ have been arylated using activated aryl halides. Substitution takes place mainly at the 1-position.

3. Amination

4,5-Diphenyl-*v*-triazole is aminated by reaction with hydroxylamine-*O*-sulfonic acid. The 1- and 2-aminotriazoles are formed in approximately equal amounts.²⁰⁶ Intramolecular amination of 1- and 2-aryltriazoles is achieved by generating a nitrene intermediate in the ortho position of the aryl substituent; for example, in the thermolysis (Scheme 42) of the azide (17).^{219a}



SCHEME 42

4. Acylation

v-Triazoles are acylated with acyl halides and anhydrides. Iso-cyanates have been used to prepare urea derivatives.²²⁰ Substitution takes place at the 1-position,^{121, 221} but the acyl group may migrate to the 2-position on heating or on treatment with base. Thus, acetylation with acetyl chloride gives 1-acetyl derivatives which rearrange to the 2-isomers above 120°; acetylation by heating the triazoles with acetic anhydride gives the 2-acetyl derivatives directly.^{45, 202} Reaction of 2-trimethylsilyl derivatives with acetyl chloride provides an alternative route to 1-acetyl derivatives.²⁰²

5. Carboxylation

Carboxylation of *C*-lithio or Grignard derivatives of triazoles gives the corresponding carboxylic acids.^{65, 218} 4-Aminotriazole has been carboxylated at the 5-position (14%) by heating with aqueous sodium bicarbonate.²²²

²¹⁹ P. N. Neuman, *J. Heterocycl. Chem.* **7**, 1159 (1970).

^{219a} R. A. Carboni and J. C. Kauer, *J. Amer. Chem. Soc.* **89**, 2633 (1967).

²²⁰ W. Benz and H. A. Staab, *Ann.* **648**, 72 (1961).

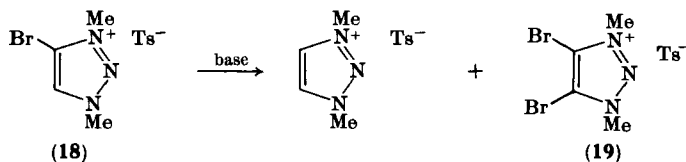
²²¹ R. Hüttel and J. Kratzer, *Chem. Ber.* **92**, 2014 (1959); J.-P. Anselme and R. Huisgen, *ibid.* **98**, 2998 (1965).

²²² N. J. Cusack, G. Shaw, and G. J. Litchfield, *J. Chem. Soc. C*, 1501 (1971).

6. Halogenation and other Electrophilic Substitution

Halogenation of *v*-triazole and several monomethyl and dimethyl derivatives has been studied.²²³ Bromination of *v*-triazole gives the 4,5-dibromo derivative; with an excess of sodium hypobromite, a 1,4,5-tribromo derivative can also be isolated. Attempted chlorination gave the hydrochloride salt instead, although 1-methyltriazole gives a 4-chloro derivative. A 1-iodo derivative, which rearranges on heating to the 4-isomer, is obtained with iodine.²²⁴

Bromination of triazolium salts and triazolium oxides has been achieved using bromine and *N*-bromoacetamide. The salt (18) itself acts as a brominating agent in basic solution, giving (Scheme 43) a mixture containing the dibromo derivative (19).^{216, 225}



SCHEME 43

Bromination of 2-phenyltriazole in the presence of silver sulfate gives the *p*-bromophenyl derivative.²²⁶ Similarly, nitration takes place first in the para position of the benzene ring, but the triazole ring is substituted on further nitration.^{92, 227} Early work by Dimroth showed that triazoles containing an activating group can undergo *C*-nitrozaion and diazo coupling.³

B. NUCLEOPHILIC SUBSTITUTION

1. Diazonium Salts

Displacement of nitrogen from diazonium salts derived from 4- or 5-aminotriazoles can be achieved in the same manner as for other aromatic diazonium salts; for example, diazotization of 4-amino-1,2,3-triazole-5-carboxamide and reaction with iodine and potassium iodide gives the 4-iodo derivative.²²⁸

²²³ R. Hüttel and G. Welzel, *Ann.* **593**, 207 (1955).

²²⁴ R. Miethchen, H. Albrecht, and E. Rachow, *Z. Chem.* **10**, 220 (1970).

²²⁵ M. Begtrup, *Acta Chem. Scand.* **25**, 249 (1971).

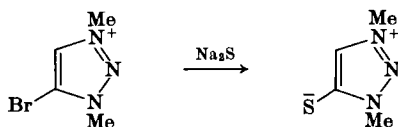
²²⁶ B. M. Lynch, *Can. J. Chem.* **41**, 2380 (1963).

²²⁷ B. M. Lynch and T. L. Chan, *Can. J. Chem.* **41**, 274 (1963).

²²⁸ Y. F. Shealy and C. A. O'Dell, *J. Med. Chem.* **9**, 733 (1966).

2. Displacement of Halide

Displacement of bromide from triazolium salts by either hydroxide or sulfide takes place readily and leads to the formation of mesoionic triazolium oxides or sulfides (e.g. Scheme 44).^{216, 217, 229, 230}



SCHEME 44

Displacement of chloride from a neutral triazole has also been reported; for example, 5-chloro-1,4-diphenyltriazole reacts with sodium cyanide in dimethyl sulfoxide to give the 5-cyano derivative.³¹

C. MIGRATIONS OF RING SUBSTITUENTS

1-Acyl- and 1-alkoxycarbonyl-1,2,3-triazoles are readily isomerized to the 2*H*-isomers in the presence of triethylamine or other bases.^{55, 87} The reaction has been shown to be intermolecular and probably involves nucleophilic attack by N-2 of one triazole on the carbonyl group attached to another. The rearrangement can also be brought about by heat (for example, 1-acetyltriazoles are isomerized to the 2*H*-isomers above 120°),²⁰² so that triazole syntheses which involve the use of bases or heat may give the 2*H*-isomers directly. For example, the triazole isolated from the thermal addition of ethyl azidoformate to phenylacetylene is 2-ethoxycarbonyl-4-phenyl-1,2,3-triazole⁵⁵ and not a 1*H*-isomer, as had been assumed earlier.¹⁰ It is likely that some other 1-alkoxycarbonyltriazole and 1-acyltriazole structures in the literature will need reassignment.

Addition of trimethylsilyl azide to acetylenes gives the 2*H*-isomers directly, and the 1*H*-isomers are not detected. A very ready migration of the trimethylsilyl group must take place in those triazoles.^{27, 45} Similar rearrangements occur in additions of trialkyltin azides.^{60a}

D. TRANSFORMATIONS OF SUBSTITUENTS^{230a}

1. Syntheses Using 4(5)-Amino-1,2,3-triazoles

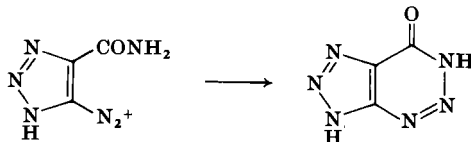
1,2,3-Triazoles bearing a *C*-amino substituent have been used as starting materials for several syntheses of biologically important com-

²²⁹ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **20**, 1555 (1966).

²³⁰ M. Begtrup, *Acta Chem. Scand.* **26**, 1243 (1972).

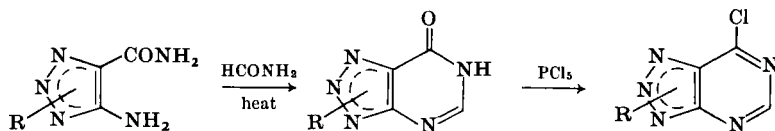
^{230a} Standard transformations involving normal reactions of substituents are not described.

pounds. Diazotization of the amino group gives diazonium salts which can undergo coupling reactions^{66, 228, 231} and which react with amines to give linear triazenes.²²⁸ Cyclization of the salts by reaction of the diazonium group with an *ortho* amido substituent provides an entry to the *v*-triazolo[4,5-*d*]-*v*-triazine ring system.^{139, 228, 231} For example, the diazonium salt from 4-amino-1,2,3-triazole-5-carboxamide is cyclized in alkaline solution, giving the triazolotriazinone (Scheme 45).²³¹



SCHEME 45

A similar route to the *v*-triazolo[4,5-*d*]pyrimidine ("8-azapurine") ring system has been developed. This involves reaction of 4-amino-1,2,3-triazole-5-carboxamide or its ring *N*-alkyl derivatives with formamide (Scheme 46).^{195, 215, 232-234} The pyrimidone derivatives thus formed can be converted into other derivatives through the chloropyrimidine (20).



SCHEME 46

(20)

Several variations of this synthetic route have been developed.²³⁵⁻²³⁷ For example, condensation of the methyltriazole (21) with thiourea gives the thiol derivative (22),²³⁶ and reaction with phosphoryl chloride in dimethylformamide converts the amino-amide to a cyano-amidine,²³⁷ which can be reduced to the 4-amino-5-aminomethyl derivative (Scheme 47).²³⁸

²³¹ Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.* **26**, 2396 (1961).

²³² A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).

²³³ A. Albert and K. Tratt, *J. Chem. Soc. C*, 344 (1968).

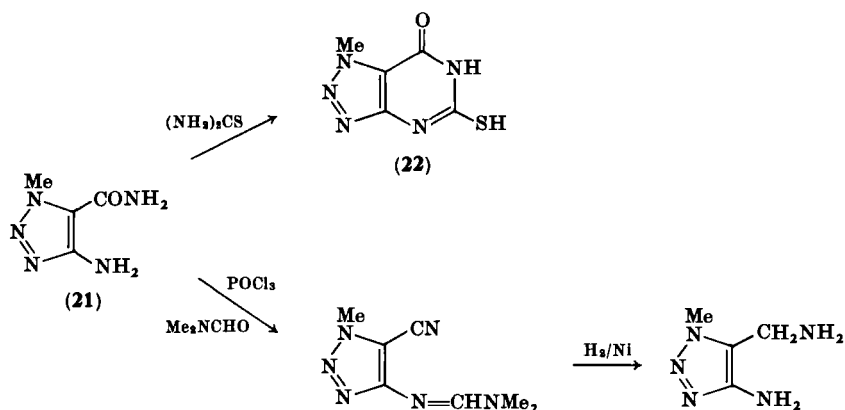
²³⁴ A. Albert, *J. Chem. Soc. C*, 152 (1969).

²³⁵ A. Albert and D. Thacker, *J. Chem. Soc., Perkin Trans. 1*, 468 (1972).

²³⁶ A. Albert and H. Taguchi, *J. Chem. Soc., Perkin Trans. 1*, 449 (1972).

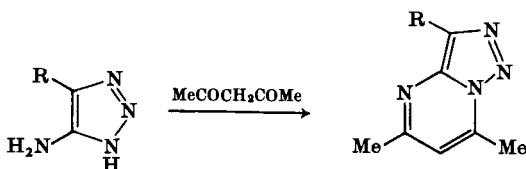
²³⁷ A. Albert, *J. Chem. Soc. C*, 230 (1970); *J. Chem. Soc., Perkin Trans. 1*, 461 (1972).

²³⁸ A. Albert, *Chem. Commun.*, 858 (1970).



SCHEME 47

Reaction of 4-amino-5-phenyl-1H-1,2,4-triazole with acetylacetone and piperidine gives a different type of fused triazole, the *v*-triazolo[3,4-*a*]pyrimidine system (Scheme 48).⁷⁷



SCHEME 48

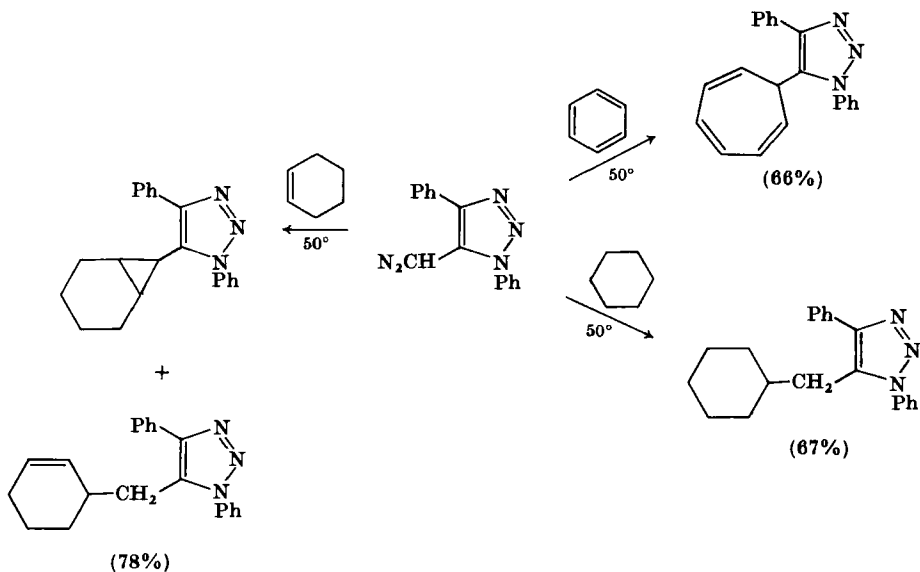
2. Other Reactions of Substituents

The properties of 5-azido and 5-diazomethyl-1,4-diphenyltriazole are unusual in that both compounds lose nitrogen under very mild conditions.^{31, 153, 181} The products derived from the azide are mainly those of ring cleavage¹⁸¹ (Section IV, G), but the diazoalkane gives a carbene which undergoes addition and insertion reactions with several solvents.³¹ These reactions are illustrated in Scheme 49.

The origin of the unusual reactivity of this system is discussed in Section IV, G. Several other useful transformations of the 5-substituents are described.³¹

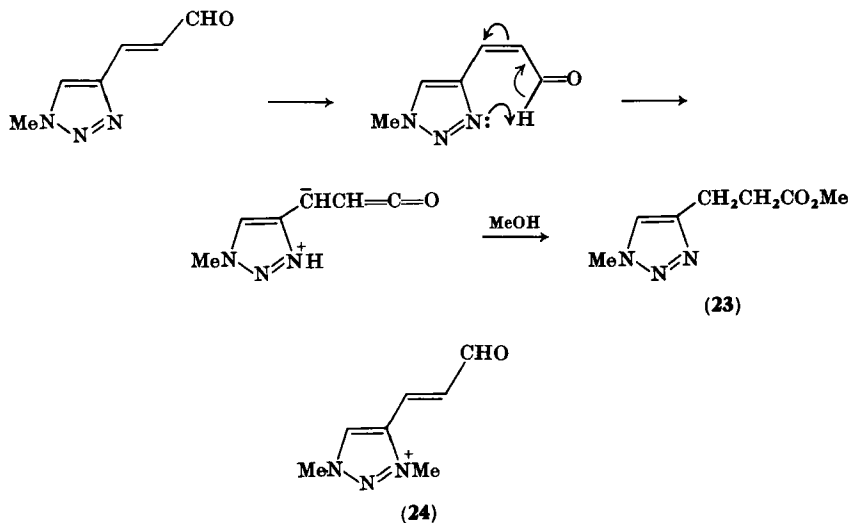
Peracetic acid oxidation of 1-benzyl-4-phenyltriazoles gives benzyloxy derivatives, possibly through an intermediate *N*-oxide.²³⁹

²³⁹ A. J. Hubert, *Bull. Soc. Chim. Belg.* **79**, 195 (1970).



SCHEME 49

Two photochemically induced reactions of substituents have been reported which require the participation of the triazole ring. Irradiation of 3-(1-methyltriazol-4-yl)acraldehyde in methanol gave the saturated ester **23** in high yield, whereas the corresponding quaternary salt **24**



SCHEME 50

gave no similar reaction. A mechanism involving participation of the lone pair at the 3-position of the triazole has been proposed (Scheme 50).²⁴⁰

A study of the photochemistry of 4-acetyl- and 4-benzoyl-5-methyl-1,2,3-triazoles²⁴¹ shows that the nature and lifetime of the lowest triplet state depends on the nature of the 1- and 4-substituents. 4-Benzoyl-5-methyl-1,2,3-triazole has a high rate constant for triplet deactivation, which is attributed to interaction of the nitrogen lone pairs with the excited carbonyl function. The compound forms a pinacol derivative when irradiated in propan-2-ol and undergoes cycloaddition, involving the carbonyl group, with 2-methylpropene, giving an oxetane derivative.

E. REMOVAL OF SUBSTITUENTS

1. Decarboxylation

Most 1,2,3-triazolecarboxylic acids lose carbon dioxide when heated above the melting point. These reactions are often useful for the preparation of simpler triazoles, for example, in the synthesis of 1-vinyl-triazoles by decarboxylation of the corresponding 4-carboxylic acids.⁷⁵ 4,5-Dicarboxylic acids normally lose 2 moles of carbon dioxide on heating above the melting point; this is so, for example, with the *v*-triazole¹⁸⁴ and with the 1-benzyltriazole;²⁴² but 1-phenyltriazole-4,5-dicarboxylic acid preferentially decarboxylates at the 5-position, giving the 4-carboxylic acid.²⁴³ 5-Methyl-1-phenyl-4-carboxylic acid is reported to be decarboxylated slowly in boiling benzene.²⁴⁴

2. Decarbonylation

1,4-Diphenyltriazole-5-carboxaldehyde is decarbonylated by treatment with sodium methoxide.³¹ The corresponding hydrazone is similarly degraded with an excess of hydrazine. In contrast, 1,5-diphenyltriazole-4-carboxaldehyde is resistant to nucleophilic decarbonylation.³¹

3. Dealkylation

1-Benzyltriazoles are readily available through cycloaddition reactions of benzyl azide. The benzyl group can be removed by reduction with

²⁴⁰ L. S. Davies and G. Jones, *Tetrahedron Lett.*, 3475 (1970).

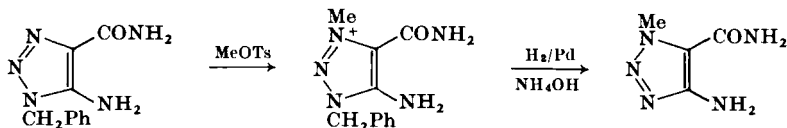
²⁴¹ J. Van Thielen, T. V. Thien, and F. C. De Schryver, *Tetrahedron Lett.*, 3031 (1971).

²⁴² R. H. Wiley, K. F. Hussung, and J. Moffatt, *J. Org. Chem.* **21**, 190 (1956).

²⁴³ O. Dimroth, *Ber.* **35**, 1031 (1902).

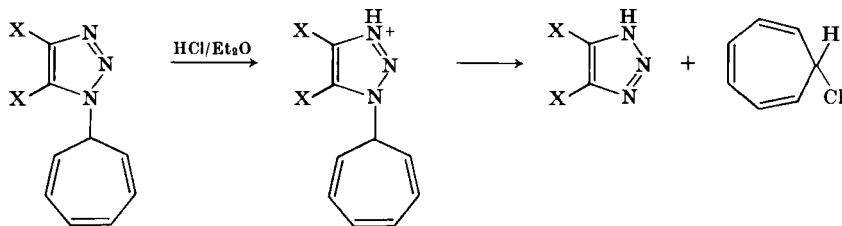
²⁴⁴ M. C. Ford and D. Mackay, *J. Chem. Soc.*, 1290 (1958).

sodium in liquid ammonia,^{35, 77, 242} by catalytic reduction,^{237, 242} by heating in piperidine,²⁴⁵ and by chromic acid oxidation,¹³⁸ thus providing a useful route to NH triazoles. An adaptation of the route can be used to prepare 1-alkyltriazaoles and is especially useful when such triazoles cannot be prepared directly from the alkyl azide. An illustration is Albert's preparation of 4-amino-1-methyltriazole-5-carboxamide from 5-amino-1-benzyltriazole-4-carboxamide (Scheme 51).²³⁷



SCHEME 51

Other alkyl groups are more difficult to remove. Begtrup has recorded examples of dealkylation of 1,2- and 1,3-dialkyltriazolium salts when they are heated, or treated with benzoyl chloride.^{230, 246} 1-Glycosyltriazaoles can be cleaved by heating with hydrochloric acid.²⁴⁷ The cleavage of 1-cycloheptatrienyltriazaoles (Scheme 52) is also brought about by acid and is probably facilitated by the stability of the tropylium ion.³⁷



SCHEME 52

4. Dearylation

N-Aryl substituents which are activated by nitro groups can be removed by nucleophilic displacement of the triazolyl anion by potassium hydroxide⁹³ or by hydrazine.⁹¹ Oxidative removal of a *p*-aminophenyl substituent by potassium permanganate has also been reported.^{3, 248}

5. Desilylation

N-Trimethylsilyl substituents are readily removed by treatment with aqueous acid.⁴⁴

²⁴⁵ J. O. Fournier and J. B. Miller, *J. Heterocycl. Chem.* **2**, 488 (1965).

²⁴⁶ M. Begtrup, *Acta Chem. Scand.* **26**, 715 (1972).

²⁴⁷ J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.*, 1651 (1958).

²⁴⁸ A. Farrington and L. Hough, *Chem. Commun.*, 219 (1965).

6. Deamination

4-Amino-1,5-diphenyltriazole is deaminated by diazotization in ethanolic solution and warming.¹⁰⁵ 1-Aminotriazoles are deaminated in high yield by treatment with nitrous acid.^{111, 113} Removal of a toluene-*p*-sulfonamido group can be accomplished in two steps by acid hydrolysis followed by diazotization, or in one step by treatment of the 1-toluene-*p*-sulfonamide derivative with sodium in liquid ammonia.²⁰⁶

7. Deacylation

1- and 2-Acyltriazoles are readily hydrolyzed in water or dilute acid; the rate constants for deacetylation of several 1-acetyltriazoles have been measured.²²¹

8. Detosylation

A 1-toluene-*p*-sulfonyl substituent is reported to be removed by boiling the triazole in ethanol.⁸⁵ Many triazole syntheses involving cycloaddition of toluene-*p*-sulfonyl azide give the NH triazole directly.

F. DIMROTH REARRANGEMENT

The thermal, acid- or base-catalyzed interconversion of 5-amino-1-phenyltriazoles and 5-anilino-1-triazoles was first observed by Dimroth. This has since been recognized as an example of a more general heterocyclic rearrangement (Scheme 53), where X and Y are hetero atoms carrying



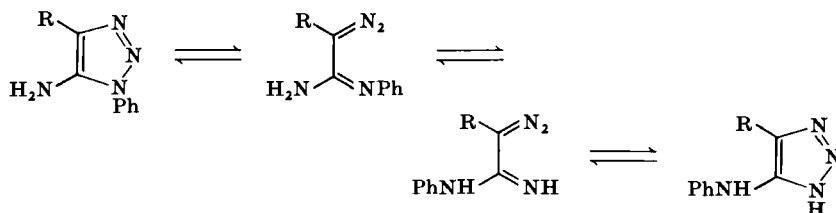
SCHEME 53

suitable substituents.²⁴⁹ In triazole chemistry, the rearrangement can lead to the synthesis of triazoles from other heterocyclic systems (Section II, E), the interconversion of triazoles, and the conversion of triazoles into other ring systems.

Studies of the interconversion of triazoles before 1960 have been summarized by Boyer.³ The equilibrium is established thermally, but its position may be influenced by the basicity of the solvent; the more

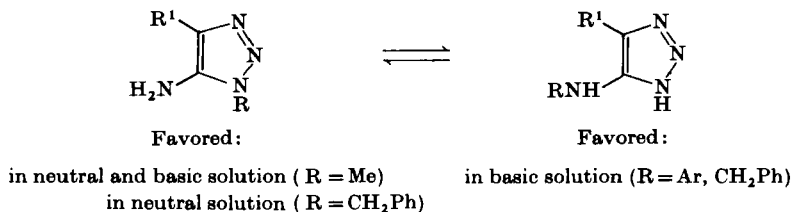
²⁴⁹ D. J. Brown, in "Mechanisms of Molecular Migrations" (B. S. Thyagarajan, ed.), Vol. 1, p. 209. Wiley (Interscience), New York, 1968; M. Wahren, *Z. Chem.* **9**, 241 (1969).

acidic NH triazoles predominate in basic media. The rearrangement probably involves a diazo-imine intermediate (Scheme 54).



SCHEME 54

Electron-attracting groups and large, rigid groups tend to favor the tautomer in which they are on the exocyclic nitrogen; alkyl groups tend to favor the cyclic nitrogen. Thus, 5-methylamino-1,2,3-triazole-4-carboxamide is completely converted into 5-amino-1-methyl-1,2,3-triazole-4-carboxamide when heated at 160° for 1 hour; the latter compound is unchanged when heated with ethanolic ammonia at 180°. ²³⁴ On the other hand, the 1-benzyl derivatives are predominantly isomerized in base, though the equilibrium favors the ring-substituted isomers in neutral conditions. ²³⁷ The results are summarized in Scheme 55.

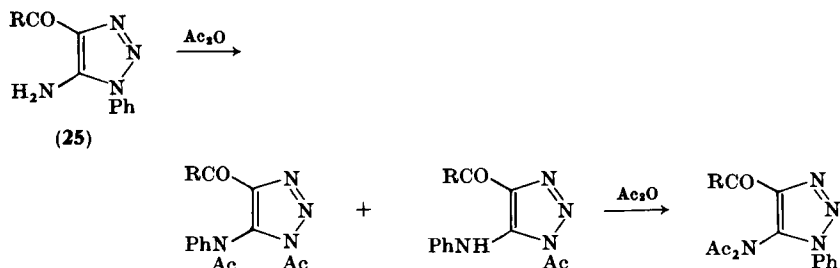


SCHEME 55

A more complex series of equilibria is established when triazoles (**25**) are heated with acetic anhydride. ⁷⁶ Brief heating gives acetyl derivatives of the rearrangement products, but longer heating gives a diacetyl derivative of the unrearranged isomer (Scheme 56). The reactions must involve deacetylation of the rearrangement products and subsequent reacetylation.

Heating 1-acetamido-4-phenyl-1,2,3-triazole with hydrochloric acid is claimed to give 5-amino-4-phenyl-1,2,3-triazole (m.p. 125°); the analogy is incorrectly drawn between this rearrangement and a Dimroth rearrangement. ²⁵⁰ The product obtained may in fact be the unrearranged 1-amino-4-phenyl-1,2,3-triazole (reported ¹¹¹ m.p. 124°).

²⁵⁰ H. El Khadem, M. A. E. Shaban, and M. A. M. Nassr, *J. Chem. Soc. C*, 2167 (1970).



SCHEME 56

5-Mercapto-1,2,3-triazoles and 5-amino-1,2,3-thiadiazoles can be interconverted by Dimroth rearrangement. Heating the thiadiazoles in basic solvents converts the thiadiazoles into triazoles, whereas the reverse reaction occurs in acidic media.^{143, 230, 251} 1-Aryl-1,2,3-triazoles rearrange more readily than 1-alkyl derivatives; for example, heating in glacial acetic acid converts 1-phenyl-5-mercapto-1,2,3-triazole into 5-phenyl-1,2,3-thiadiazole, whereas the 1-methyltriazole is unchanged in these conditions, the rearrangement taking place only in hydrochloric acid.²³⁰ Thermal equilibration of thiadiazoles and triazoles, with both isomers present, has also been observed.^{141, 142} The behavior of 5-hydroxy-1,2,3-triazoles is similar; in acidic media they rearrange to diazoacetamides. Again, the 1-aryl triazoles rearrange more readily than the 1-alkyl derivatives.²⁵²

G. REACTIONS INVOLVING CLEAVAGE OF THE TRIAZOLE RING

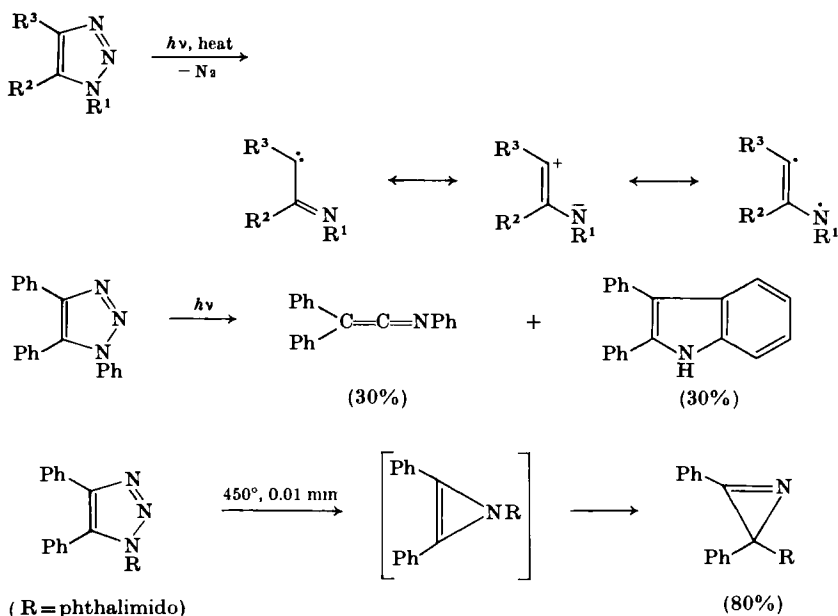
The ring system of monocyclic 1,2,3-triazoles is, in general, remarkably resistant to cleavage (although fused triazoles in which the second ring is attached at the 1- and 5-positions of the triazole are much more labile⁷⁷). The ring is not normally cleaved by oxidation or hydrolysis, and reductive cleavage only occurs under forcing conditions.⁸ There are several examples of photochemical extrusion of nitrogen from the ring; thermal extrusion of nitrogen has also been observed, but usually requires vigorous conditions.

There are several exceptions to these generalizations which depend on the presence of particular substituents, in that the substituents, or intermediates derived from them, have a destabilizing effect on the ring system. Typical reactions of monocyclic triazoles are described first, and the exceptional systems, involving "substituent-assisted" cleavage, are then discussed.

²⁵¹ M. Regitz and H. Scherer, *Chem. Ber.* **102**, 417 (1969).

1. *Thermolysis and Photolysis*

The intermediate produced by loss of nitrogen from a 1*H*-triazole can be written as an imino-carbene, as a zwitterion, or as a diradical. Subsequent reactions of the intermediate which have been observed (Scheme 57) include (a) photochemical Wolff rearrangement²⁵³ (suggesting that the intermediate may have a singlet carbene structure);



SCHEME 57

(b) ring closure involving the substituent R' (when R' is phenyl,²⁵³ benzoyl,³⁵ or 2-pyrimidinyl²⁵⁴); and (c) ring closure to form a 1*H*-azirine, followed by rearrangement to a 2*H*-azirine isomer (when R' is phthalimido¹¹⁶). The last reaction appears to be a more favorable process than Wolff rearrangement, since no ketenimines are formed in this case.

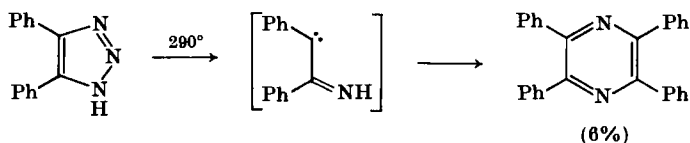
Photolysis and pyrolysis of 4-phenyltriazole gives mainly phenyl-acetonitrile;²⁵⁵ pyrolysis of 4,5-diphenyltriazole in solution gives 2,3,5,6-tetraphenylpyrazine, which is formally derived from the triazole by loss of nitrogen, dimerization, and oxidation (Scheme 58).²⁵⁵

²⁵² J. E. Leffler and S.-K. Liu, *J. Amer. Chem. Soc.* **78**, 1949 (1956).

²⁵³ E. M. Burgess, R. Carithers, and L. McCullagh, *J. Amer. Chem. Soc.* **90**, 1923 (1968).

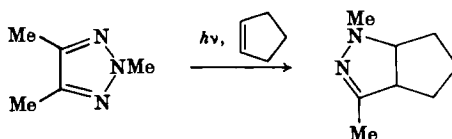
²⁵⁴ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 3811 (1970).

²⁵⁵ R. Selvarajan and J. H. Boyer, *J. Heterocycl. Chem.* **9**, 87 (1972).



SCHEME 58

Little is known about the modes of thermal and photochemical cleavage of 2*H*-triazoles. 2,4,5-Triphenyltriazole is reported to be photostable, but 2,4,5-trimethyltriazole gives acetonitrile (22%) and several other products when irradiated in ether.²⁵⁶ In cyclopentene, an adduct to be expected from a nitrilimine intermediate is isolated (Scheme 59).

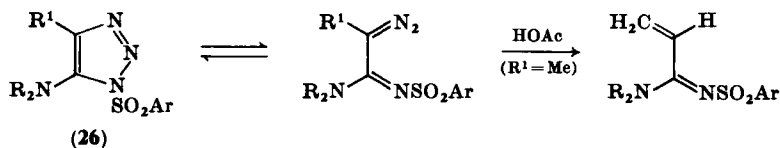


SCHEME 59

2. Substituent-Assisted Cleavage

a. *Ring-Chain Tautomerism*. 1-Cyano- and 1-arenesulfonyl derivatives of 1,2,3-triazoles undergo ready and reversible ring opening to diazo-imine tautomers. The equilibrium between 1-cyanotriazole and its open-chain isomer⁵³ is markedly temperature-dependent: At -60° in solution the NMR spectrum corresponds to that of the cyclic isomer, but on warming to 80° , complex changes in the spectra are observed. At the higher temperature the compound exists mainly as a mixture of syn and anti forms of the open structure. The infrared spectrum of the compound in the melt (35°) also shows absorptions typical of a diazo group. Chemical reactions consistent with both structures are observed; for example, anhydrous hydrogen chloride gives the hydrochloride of 1,2,3-triazole, whereas aqueous hydrogen chloride gives nitrogen and chloroacetaldehyde. The adduct of ethoxyacetylene and cyanogen azide exists entirely in the open-chain form.⁵³

With the arenesulfonyltriazoles (**26**),^{15, 16} polar, protic solvents, and electron-withdrawing substituents in the aryl group tend to favor the

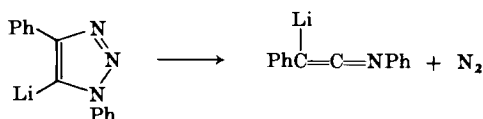


SCHEME 60

²⁵⁶ T. S. Cantrell and W. S. Haller, *Chem. Commun.*, 977 (1968).

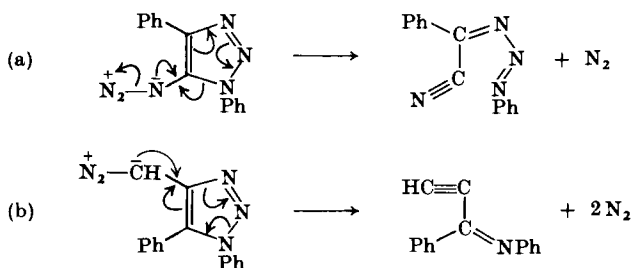
open-chain structures, which show absorptions in the infrared at about 2070 cm^{-1} (KBr). Reaction with acetic acid results in loss of nitrogen (Scheme 60).

b. *Ring Cleavage of 5-Lithiotriazoles.* 1-Phenyltriazoles which are unsubstituted at the 5-position readily undergo lithiation at this position. The 5-lithio derivatives are labile and cleave at about 40° – 50° to give lithio derivatives of ketenimines by loss of nitrogen (Scheme 61).²¹⁸



SCHEME 61

c. *Cleavage of Amino-, Azido-, and Diazomethyltriazoles.* 5-Azido-1,4-diphenyltriazole has been shown to be unusually labile: Above about 50° , nitrogen is evolved and a conjugated nitrile is formed.^{153, 181} The reaction can be represented as a concerted process, and the ease of the reaction supports the view that the loss of nitrogen is assisted by opening of the ring (Scheme 62a). The corresponding diazomethyl compound is



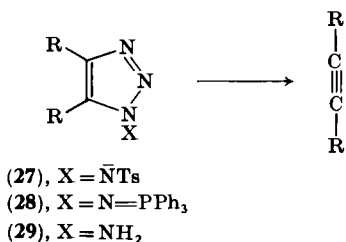
SCHEME 62

also unusually labile,³¹ but in this case, the open structure cannot be detected (though it may be formed initially as a less favorable valence tautomer of the carbene^{256a}). The isomeric 4-diazomethyl compound undergoes ring cleavage with loss of two molecules of nitrogen (Scheme 62b).

The sequence is completed by 1-aminotriazoles and their derivatives, which undergo complete fragmentation with loss of two molecules of

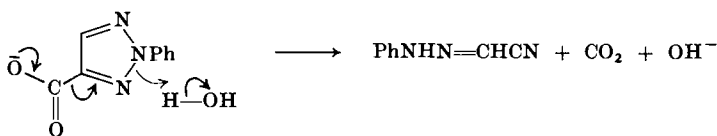
^{256a} An analogous ring cleavage of a 2-diazoalkylfuran has been observed to give an open-chain acetylene [R. V. Hoffman and H. Shechter, *J. Amer. Chem. Soc.* **93**, 5940 (1971)].

nitrogen on decomposition. Thus, photolysis of salts of 1-toluene-*p*-sulfonamidotriazoles (27)²⁵⁷ or of iminophosphoranes (28),²⁵⁸ and oxidation of 1-aminotriazoles (29),¹¹⁵ have been used as a route to acetylenes (Scheme 63). This method is especially useful for strained cyclic acetylenes which have only a transient existence. Cycloheptyne and cyclohexyne have been generated in this way.



SCHEME 63

d. *Decarboxylation with Ring Cleavage.* Heating 2-phenyltriazole-4-carboxylic acid with barium hydroxide causes decarboxylation and cleavage of the triazole ring.²⁵⁹ The cleavage can be represented as a concerted process, involving a molecule of water of hydration (Scheme 64).



SCHEME 64

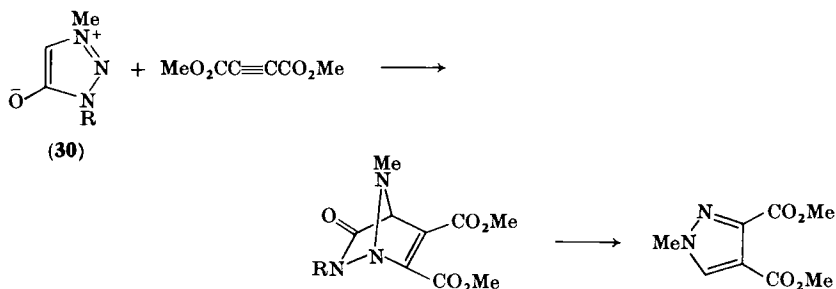
e. *Cycloaddition.* The mesoionic triazole (30, R = *p*-MeC₆H₄) undergoes cycloaddition reactions with diethyl azodicarboxylate and with dimethyl acetylenedicarboxylate. In the latter case, the initial adduct fragments to dimethyl 1-methylpyrazole-3,4-dicarboxylate and *p*-tolyl isocyanate (Scheme 65).¹⁵⁴ The dimethyl derivative (30, R = Me) is more reactive and undergoes a cycloaddition reaction with phenyl isocyanate.²⁶⁰ Cycloadditions involving a mesoionic triazolo imine have also been observed.^{158a}

²⁵⁷ F. G. Willey, *Angew. Chem. Int. Ed. Engl.* **3**, 138 (1964).

²⁵⁸ F. J. Graveling, Ph.D. Thesis, University of Leicester, 1969.

²⁵⁹ R. M. Carman, D. J. Brecknell, and H. C. Deeth, *Tetrahedron Lett.*, 4387 (1966); D. J. Brecknell, R. M. Carman, H. C. Deeth, and J. J. Kirby, *Aust. J. Chem.* **22**, 1915 (1969).

²⁶⁰ K. T. Potts and S. Husain, *J. Org. Chem.* **37**, 2049 (1972).



SCHEME 65

H. SALTS AND COMPLEXES^{260a}

Iron complexes are reported to be formed from 4-benzoyl- and 4-butyryltriazole and ferrous chloride²⁶¹ or nonacarbonyl diiron.²⁶² The complexes from nonacarbonyl diiron have two triazole molecules per atom of iron, with the iron π -bonded to the ring.

A 1:1 complex of a 4-aryltriazole with triphenylphosphine oxide is also reported.⁸⁷

ACKNOWLEDGMENT

The authors thank Professor C. W. Rees for his interest and encouragement in this project.

^{260a} For work published before 1960, see Boyer.³

²⁶¹ R. A. Stukan, V. I. Gol'danskii, E. F. Makarov, B. V. Borshagovskii, N. S. Kochetkova, M. I. Rybinskaya, and A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR* **170**, 354 (1966) [*Chem. Abstr.* **66**, 60555 (1967)].

²⁶² A. N. Nesmeyanov, M. I. Rybinskaya, N. S. Kochetkova, V. N. Babin, and G. B. Shul'pin, *Dokl. Akad. Nauk SSSR* **181**, 1397 (1968); [*Chem. Abstr.* **69**, 113021 (1968)].

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Nitrogen-Bridged Six-Membered Ring Systems: 7-Azabicyclo[2.2.1]hepta-2,5-dienes, Naphthalen-1,4- imines, and Anthracen-9,10-imines

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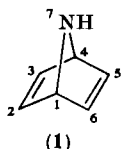
I. Introduction

The chemistry of the bicyclo[2.2.1]heptane ring system, with and without double bonds in the two-carbon bridges, includes many well-known and interesting features which illustrate important stereochemical aspects of some organic reaction mechanisms. Among derivatives of

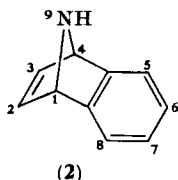
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this ring system containing a heteroatom at the 7-position, 7-oxabicyclo[2.2.1]heptanes have been most extensively studied, but the less accessible nitrogen-containing analogs have received attention only recently. The chemistry of 7-azabicyclo[2.2.1]heptadienes, of mono- and dibenzo derivatives and of hydro derivatives of this ring system is the subject of review, in which appropriate comparisons are cited to the behavior of analogous ring systems containing other heteroatoms.

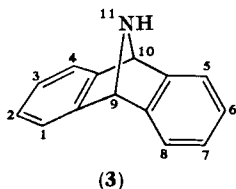
The approved *Chemical Abstracts* names and numbering of the ring systems are shown in structures 1–3. (Some of the other names given in parentheses are currently used in different chemical journals.)



7-Azabicyclo[2.2.1]hepta-2,5-diene
(7-Azanorbornadiene)

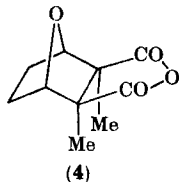


Naphthalen-1,4-imine
(Naphthalen-1,4-endamine)
(1,4-Epiminonaphthalene)
(7-Azabenzonorbornadiene)
(2,3-Benzo-7-azabicyclo[2.2.1]hepta-2,5-diene)



Anthracen-9,10-imine
(Anthracen-9,10-endamine)
(9,10-Epiminoanthracene)
(7-Azadibenzonorbornadiene)
(Dibenzo-7-azabicyclo[2.2.1]hepta-2,5-diene)

A structure proposed¹ for the lycopodium alkaloid, annotinine, was a derivative of 7-azabicyclo[2.2.1]heptane, but this is incorrect,² and no naturally occurring compound is known to contain this ring system. On the other hand, the 7-oxabicyclo[2.2.1]heptane ring system is present



¹ F. A. L. Anet and L. Marion, *Can. J. Chem.* **33**, 849 (1955).

² R. F. H. Manske, in "The Alkaloids" (R. F. H. Manske, ed.), Vol. VII, Chapter 23. Academic Press, New York, 1960, and references therein.

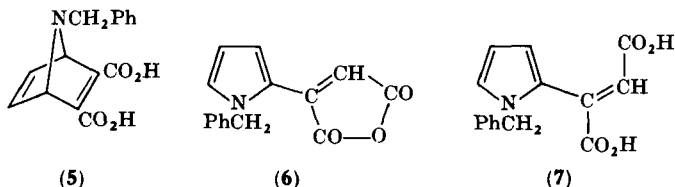
in cantharidin (4),³ the irritant principle of the Spanish fly, and many other derivatives have biological activity either in animals^{4, 5} or in plants.⁶

II. 7-Azabicyclo[2.2.1]heptanes and 7-Azabicyclo[2.2.1]heptadienes

A. SYNTHESSES

1. 7-Azabicyclo[2.2.1]hepta-2,5-dienes

The first derivative of this ring system to be prepared was the adduct (5), obtained from *N*-benzylpyrrole and acetylenedicarboxylic acid in refluxing ether, but as a minor product together with the products (6) and (7) of Michael addition at the 2-position of the pyrrole.⁷⁻⁹ The compounds 8-10 were similarly prepared,¹⁰⁻¹² but also only in low yield



(see Table I). [The *N*- α -naphthylmethyl compound (8) is elsewhere¹³⁻¹⁵ mistakenly described as an adduct of *N*- α -naphthylpyrrole with

³ G. Stork, E. E. van Tamelen, L. J. Friedman, and A. W. Burgstrahler, *J. Amer. Chem. Soc.* **75**, 384 (1953).

⁴ E. R. Bockstahler, U.S. Patent 3,261,845 (1966); *Chem. Abstr.* **65**, P15325g (1966).

⁵ L. M. Rice and C. H. Grogan, *J. Org. Chem.* **25**, 393 (1960).

⁶ Numerous references to derivatives of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid as defoliants, herbicides, fungicides, etc., are cited in index volumes of *Chem. Abstr.* since Vol. **46** (1952).

⁷ L. Mandell and W. A. Blanchard, *J. Amer. Chem. Soc.* **79**, 2343, 6198 (1957).

⁸ O. Cervinka, K. Pelz, and I. Jirkovsky, *Collect. Czech. Chem. Commun.* **26**, 3116 (1961).

⁹ A. Shaf'ee and G. Hite, *J. Org. Chem.* **33**, 3435 (1968).

¹⁰ L. Mandell, J. U. Piper, and C. E. Pesterfield, *J. Org. Chem.* **28**, 574 (1963).

¹¹ R. Kitzing, R. Fuchs, M. Joyeux, and H. Prinzbach, *Helv. Chim. Acta* **51**, 888 (1968).

¹² R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1008 (1963).

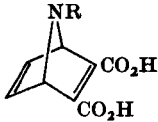
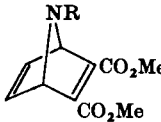
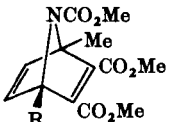
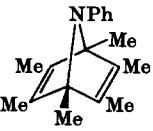
¹³ J. Sauer, *Angew. Chem. Int. Ed. Engl.* **5**, 211 (1966).

¹⁴ M. G. Barlow, R. N. Haszeldine and R. Hubbard, *Chem. Commun.*, 301 (1969); *J. Chem. Soc. C*, 90 (1971).

¹⁵ R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.* **47**, 2391 (1969).

acetylenedicarboxylic acid or its diester.] The failure to obtain a corresponding adduct from *N*-triphenylmethylpyrrole (also wrongly reported elsewhere^{13, 14}) led to the discounting¹⁰ of an earlier suggestion⁷ that the size of the *N*-substituent was responsible for the occurrence of the Diels–Alder addition, which was previously unknown with pyrroles.

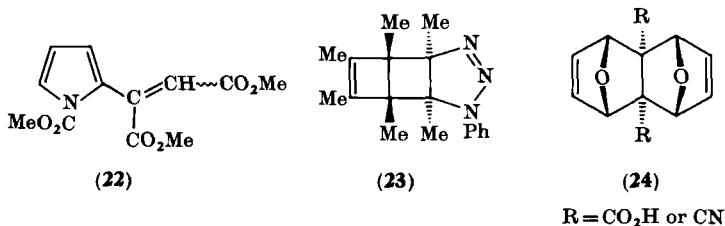
TABLE I
7-AZABICYCLO[2.2.1]HEPTA-2,5-DIENE DERIVATIVES

Structure	Yield (%)	References	Structure	Yield (%)	References
					
(5) R = CH ₂ Ph	8–18	7–9	(11) R = CO ₂ Me	42, 90	11, 15
(8) R = CH ₂ - α -C ₁₀ H ₇	9	10	(12) R = COMe	45 ^a	11
(9) R = Me	10	11	(13) R = CONH ₂	36	11
(10) R = CO ₂ Me	6	12	(14) R = Ts	30	11
			(15) R = Ph	25 ^a	11
(19) R = H	50–60	16	(16) R = <i>p</i> -ClC ₆ H ₄	25	11
(20) R = Me	85–90	16	(17) R = <i>p</i> -BrC ₆ H ₄	25	11
			(18) R = <i>p</i> -O ₂ NC ₆ H ₄	64	11
(21)	12	17			

^a Impure product due to decomposition.

With an electron-withdrawing *N*-substituent the pyrrole ring is more reactive as a diene towards acetylenic dienophiles, and the Diels–Alder

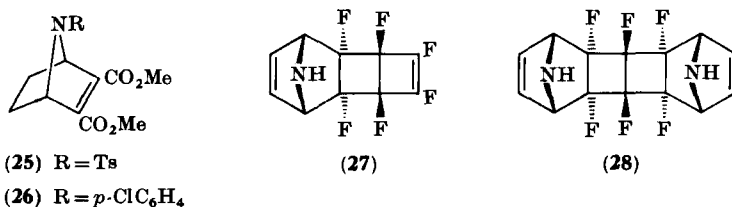
adducts (11–20) have been obtained with dimethyl acetylenedicarboxylate^{11, 15, 16} (see Table I). The yield of the bicyclic triester (11) is increased at the expense of the isomeric *cis*- and *trans*-Michael adducts (22) in the presence of a Lewis acid catalyst (aluminum trichloride or boron trifluoride),¹⁵ which complexes with the product (11) and may also deactivate the pyrrole ring to electrophiles while enhancing its reactivity as a diene. *N*-Phenyl-1,2,3,4,5,6-hexamethyl-7-azabicyclo[2.2.1]hepta-2,5-diene (21) has been reported¹⁷ as an unusual product of the decomposition of the tricyclic triazoline (23) at 195°.



7-Oxabicyclo[2.2.1]hepta-2,5-dienes are usually obtainable in good yield by addition of acetylenic dienophiles to furans, although 1:2 adducts, e.g., 24, result in some cases^{18, 19} since furans also add readily to derivatives of maleic acid. The parent compounds, 7-aza- and 7-oxabicyclo[2.2.1]hepta-2,5-diene, are still unknown.

2. 7-Azabicyclo[2.2.1]hept-2-enes

The dihydro derivatives 25 and 26 are obtained¹¹ from 14 and 16, respectively, by selective catalytic hydrogenation of the unsubstituted double bond; the diacid (5) likewise gives a dihydro derivative (57)⁷ (see Section II, D).



¹⁶ R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.* **48**, 1472 (1970).

¹⁷ L. A. Paquette and R. J. Haluska, *J. Amer. Chem. Soc.* **94**, 534 (1972).

¹⁸ O. Diels, K. Alder, H. Nienburg, and O. Schmalbeck, *Ann.* **490**, 243 (1931).

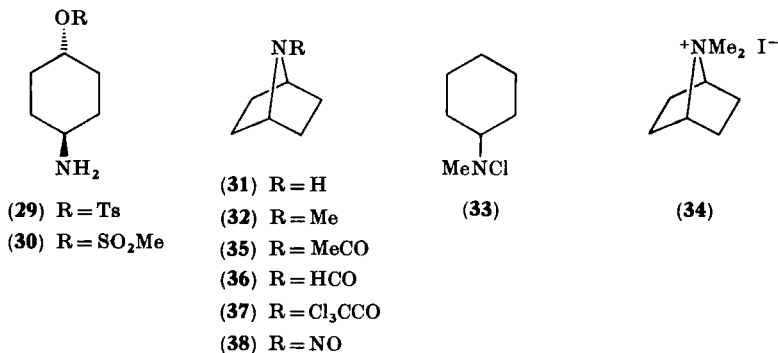
¹⁹ H. Stockman, *J. Org. Chem.* **26**, 2025 (1961); C. D. Weis, *ibid.* **28**, 74 (1963).

Although pyrroles do not generally participate in Diels–Alder reactions with olefinic dienophiles, the very reactive hexafluoro-Dewar benzene with pyrrole gives the 1:1 and 1:2 adducts, **27** and **28**, both of which probably have all-*exo* stereochemistry.¹⁴ Some other 7-azabicycloheptene derivatives have been obtained via cycloaddition reactions of 7-azaquadricyclanes (see Section II, F).

3. 7-Azabicyclo[2.2.1]heptanes

Three different synthetic routes have afforded derivatives of the saturated 7-azabicyclo[2.2.1]heptane ring system.

a. *From Cyclohexylamine Derivatives.* The parent compound (**31**) was first obtained by treatment of *cis*- and *trans*-4-bromocyclohexylamine with hot alkali,²⁰ but separation of a pure product was difficult, and it appears in the light of recent work²¹ that the original identification of the picrates of **31** and of the isomeric 4-aminocyclohexene was probably mistaken. The *trans*-4-aminocyclohexyl sulfonate esters (**29** and **30**) in alkaline aqueous ethanol gave high yields of **31**, isolated as its hydrochloride,²¹ thereby completing a successful synthesis (12 or 36% overall yield) of **31** from *p*-acetamidophenol.



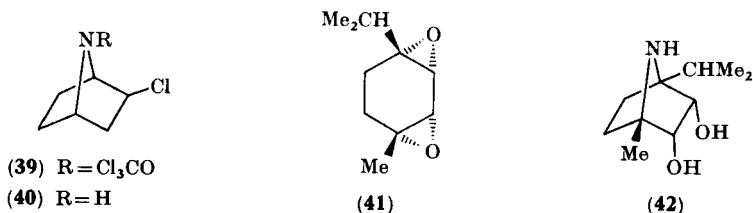
The *N*-methyl derivative (**32**) was obtained from **31** via a Leuckart reaction and isolated as its hydrochloride;²¹ **32** is also formed in the Hoffmann–Löffler reaction (photolysis in sulfuric acid) of the *N*-chloramine (**33**), since after separation of secondary amines and addition of methyl iodide a 10% yield of the methiodide (**34**) was obtained.²² The secondary amine (**31**) was also converted to its *N*-acyl and *N*-nitroso derivatives (**35–37**) and (**38**), respectively, by conventional procedures.²¹ Free-radical chlorination of **37** gave the *exo*-2-chloro derivative (**39**) and

²⁰ J. von Braun and K. Schwarz, *Ann.* **481**, 56 (1930).

²¹ R. R. Fraser and R. B. Swingle, *Can. J. Chem.* **48**, 2065 (1970).

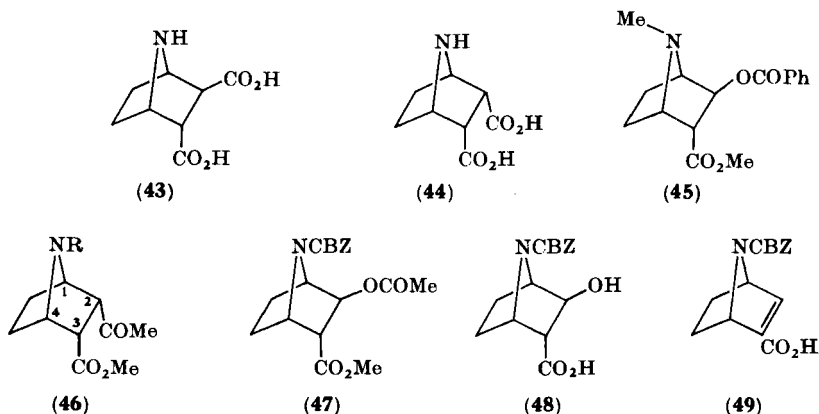
²² E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **82**, 1657 (1960).

unidentified dichloro derivatives.²¹ Hydrolysis of **39** gave **40**, isolated as its hydrochloride, but attempted dehydrochlorination of **40** to give 7-azabicyclo[2.2.1]hept-2-ene was unsuccessful.



Ammonolysis of pseudoascaridole (**41**) gave the diol (**42**)²³ rather than an isomeric 7-oxabicyclo[2.2.1]heptane derivative as suggested earlier. A likely mechanism for the formation of **42** would result in the hydroxyl groups being *cis*, *endo*, and the spin-spin coupling constant between protons attached to C-2 and C-3 confirms the *cis* configuration. The *N*-methyl derivative of (**42**) is obtained from **41** with methylamine.²³

b. *By Hydrogenation*. Complete catalytic hydrogen of **5** results in the saturation of both double bonds and hydrogenolysis of the *N*-benzyl group,^{7,9} giving a mixture of diastereoisomeric diacids (**43**) and (**44**). The *cis*, *endo* compound (**44**) is the starting material for a lengthy synthesis of pseudo-4-norcocaine (**45**),⁹ in which three points deserve special



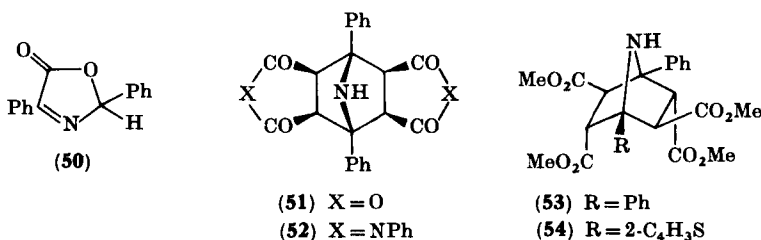
R = CBZ or Ts

comment. Assignment of *exo* or *endo* stereochemistry to substituents at C-2 and C-3 throughout this series of compounds relied heavily on the evidence of NMR spectra (see Section II, B). The *endo*-2-acetyl-*endo*-3-carboxylate esters (**46**) epimerized at C-2 on treatment with dilute acid.

²³ A. Runquist, G. Pierson, and O. Runquist, *J. Org. Chem.* **34**, 3192 (1969).

Saponification of the diester (47) gave the hydroxyacid (48) along with its dehydration product, the 7-azabicyclo[2.2.1]heptene (49).

c. *From Azlactones.* Huisgen *et al.*²⁴ have described 1,3-dipolar cycloaddition reactions of azlactones which lead to the formation of polysubstituted 7-azabicyclo[2.2.1]heptane derivatives. The mechanism of these reactions involves tautomerization of the azlactone to a meso-ionic oxazolium 5-oxide,²⁵ which adds stepwise two molecules of an olefinic dipolarophile with concomitant decarboxylation. Thus, from the 2,4-diphenyloxazolin-5-one (50) the adducts 51 and 52 were obtained with maleic anhydride and *N*-phenylmaleimide, respectively; 50 and dimethyl fumarate at 130° gave the 1:2 adduct 53, and analogous adducts were obtained with several other dipolarophiles. The stepwise addition mechanism is confirmed by the formation of a 1:1:1 adduct (less carbon dioxide) from 50 with acenaphthene and dimethyl fumarate. Several of these adducts have been patented for possible applications in the synthesis of pharmaceuticals.²⁶



The stereochemical characterization of the adduct 53 follows from its NMR spectrum and a comparison with that of the 1-(2-thienyl) compound (54). The all-*exo* configuration for the adducts 51 and 52 is consistent with the NMR spectra (hydrogen atoms at C-2, C-3, C-5, and C-6 all equivalent), with the proposed mechanism of formation, and with the failure of the related tetramethyl ester to undergo *N*-acetylation even in very vigorous conditions.²⁴ *N*-substituted derivatives of compounds such as 51–53 may be obtainable directly from similar dipolar cycloaddition reactions of mesoionic *N*-substituted oxazolium 5-oxides, although the formation of only the *N*-methyl derivative of (52) has so far been reported.²⁷

²⁴ R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tetrahedron Lett.*, 481 (1964); *Chem. Ber.* **103**, 2368 (1970).

²⁵ H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.* **92**, 4340 (1970).

²⁶ Union Carbide Corp., British Patent 1,098,356 (1968); *Chem. Abstr.* **69**, P19037p (1968).

²⁷ H. Gotthardt and R. Huisgen, *Chem. Ber.* **103**, 2625 (1970).

B. PHYSICAL AND SPECTROSCOPIC CHARACTERISTICS

In the UV absorption spectra of the 7-azabicyclo[2.2.1]heptadiene-2,3-diester (11)–(14), a maximum or shoulder between 290–300 nm ($\epsilon \sim 10^3$) is attributable to interaction between the homoconjugated double bonds.¹¹ This band is absent from the spectrum of the 5,6-dihydro derivative (25),¹¹ but absorption in the same position has been recorded for similarly substituted 7-oxabicyclo[2.2.1]heptadiene derivatives.²⁸

In the NMR spectra of 7-azabicyclo[2.2.1]heptadienes, with identical substituents at C-2 and C-3 as in structure 9, the bridgehead protons couple with the vinylic protons at C-5 and C-6 in a degenerate A_2X_2 system such that their two signals appear as triplets.¹¹ This is likewise characteristic of carbocyclic norbornadiene derivatives.²⁹

In the NMR spectra of 7-azabicyclo[2.2.1]heptane derivatives, the apparent absence of spin–spin coupling between the bridgehead protons and endo protons at C-2 and C-3 ($J < 1\text{ Hz}$) is a consequence of the dihedral angle between the respective C–H bonds being $\sim 80^\circ$.³⁰ Exo-Protons at C-2 and C-3, however, couple observably with those at the adjacent bridgehead positions, and this difference has proved very useful for assignment of exo or endo stereochemistry to substituents.^{9, 21} The same situation applies to bicyclo[2.2.1]heptane³¹ and 7-thiabicyclo[2.2.1]heptane³² derivatives, which clearly have very similar geometry.

The basicity of 7-azabicyclo[2.2.1]heptane (31) (pK_a 10.8 for its conjugate acid in water at 25°)²¹ is little indication of the effect of ring strain, since azetidine and pyrrolidine have similar values.

C. CONFIGURATIONAL CHANGES AT THE NITROGEN ATOM

In cyclic amines rigidity of the ring and a small angle between the C–N bonds characteristically result in a relatively high energy barrier to inversion of configuration at the nitrogen atom. The effect is most marked for aziridine derivatives, for which the kinetics of inversion processes are conveniently studied by variable-temperature NMR

²⁸ P. Vogel, B. Wilhalm, and H. Prinzbach, *Helv. Chim. Acta* **52**, 584 (1969).

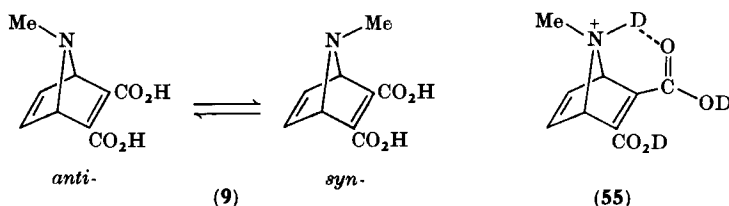
²⁹ E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.* **86**, 1166 (1964).

³⁰ M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

³¹ F. A. L. Anet, *Can. J. Chem.* **39**, 789 (1961). Many other references are summarized by P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.* **86**, 1171 (1964).

³² E. J. Corey and E. Block, *J. Org. Chem.* **31**, 1663 (1966).

spectroscopy.³³ In the NMR spectrum¹¹ of the 7-azabicyclo[2.2.1]-heptadiene derivative (9) in dimethyl sulfoxide-*d*₆ at 36° both the vinylic protons at C-5 and C-6 and those of the *N*-methyl group give pairs of resonance signals, which coalesce to single signals at ~96°. The more intense component of each pair (~2:1) is that at higher field, which is ascribed to the less-hindered anti isomer.¹¹ The coalescence at higher temperature is due to more rapid syn ⇌ anti inversion, whereby averaged signals are recorded. A lower coalescence temperature was found for the *N*-benzyl compound (5) in pyridine-*d*₅,³⁴ but it has been suggested that the inversion energy barrier for *t*-amino acids is artificially high in nonbasic solvents due to protonation of the nitrogen atom. In the spectrum of 9 in trifluoroacetic acid-*d* the intense signals for the vinylic and *N*-methyl protons are each accompanied by a weak satellite at lower field (intensity ratio ~40:1),¹¹ which suggests that a stereoselective deuteration occurs, probably to give 55.



In the *N*-acetyl-7-azabicyclo[2.2.1]heptadiene derivative (12), restricted rotation about the N-CO bond makes the bridgehead hydrogen atoms at C-1 and C-4 nonequivalent, so that they give rise to two equal intensity signals in the NMR spectrum.¹¹ *N*-Acetyl- and *N*-nitroso-7-azabicyclo[2.2.1]heptanes [(35) and (38)] show the same effect. From the coalescence temperatures (>50°) the free energy barriers to internal rotation were calculated to be 17.4, 17.1, and 16.5 kcal mole⁻¹ for 12, 35, and 38, respectively.^{21, 34} These values are slightly lower than those measured for analogous acyclic amine derivatives, *N,N*-dimethylacetamide and *N,N*-dimethylnitrosamine, respectively.

D. THERMAL STABILITY

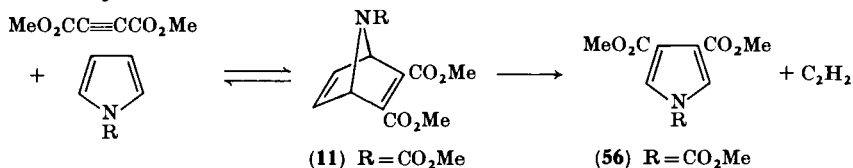
The thermal lability of 7-azabicyclo[2.2.1]heptadiene derivatives is the main factor limiting their availability by synthesis (see Section II,

³³ A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.* **80**, 5203 (1958); A. Leuvenstein, J. F. Neumer, and J. D. Roberts, *ibid.* **82**, 3599 (1960); M. Jautelat and J. D. Roberts, *ibid.* **91**, 642 (1969).

³⁴ W. J. Deloughry and I. O. Sutherland, *Chem. Commun.* 1104 (1971).

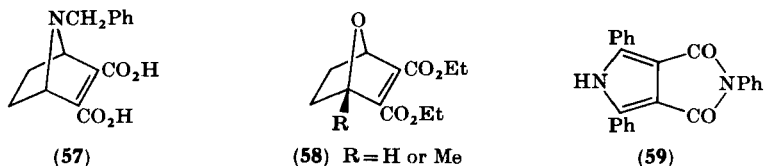
A,1). The thermal stability with respect to retro-Diels–Alder reaction of those derivatives with ester groups at the 2- and 3-positions increases with increasing electron withdrawal by the N-substituent. Prinzbach *et al.*¹¹ made revealing comparisons of the decomposition of the adducts **15–18** at 65° which support this generalization. The diacid (**5**) decomposed in refluxing aqueous sodium carbonate to regenerate *N*-benzylpyrrole:⁷ some of the anhydride (**6**) was also obtained on acidification of the reaction mixture.

At higher temperatures retro-Diels–Alder reaction may also occur in the opposite sense to addition, as in the reaction of methyl pyrrole-1-carboxylate with dimethyl acetylenedicarboxylate at 200°, which affords acetylene and the pyrrole triester (**56**).³⁵ The decomposition of the suspected intermediate Diels–Alder adduct (**11**) at 170° has been separately established.¹⁵ Compounds **19** and **20** are intermediates in similar addition–elimination reactions leading to pyrrole-1,3,4-triesters,³⁶ in which removal of acetylene from the system makes the reaction sequence effectively irreversible.



Attempted esterification of the 7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylic acids (**5**) and (**10**) with diazomethane in mild conditions led to decomposition liberating the corresponding pyrroles.^{8, 12} Dimethyl acetylenedicarboxylate, the other decomposition product, reacted further with an excess of diazomethane to give dimethyl pyrazole-4,5-dicarboxylate and an *N*-methyl derivative.^{8, 12}

The 7-azabicyclo[2.2.1]heptene derivative (**57**) decomposes in hot aqueous sodium carbonate solution to give *N*-benzylpyrrole-3,4-dicarboxylic acid⁷ and, presumably, ethylene. Furan-3,4-dicarboxylic acid derivatives are formed analogously on heating the 7-oxabicyclo[2.2.1]heptene diesters (**58**).³⁷ The only thermal decomposition of a



³⁵ R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 457 (1961).

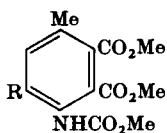
³⁶ N. W. Gabel, *J. Org. Chem.* **27**, 301 (1962).

³⁷ K. Alder and H. F. Rickert, *Ber.* **70B**, 1354 (1937).

7-azabicyclo[2.2.1]heptane derivative recorded is that of compound **52** at 300° in the presence of palladium on charcoal, which afforded the pyrrole-3,4-dicarboximide (**59**).²⁴

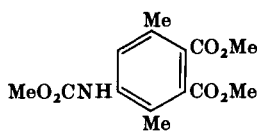
E. AROMATIZATION OF 7-AZABICYCLO[2.2.1]HEPTADIENES

In the presence of aluminum trichloride at 40° the 7-azabicyclo[2.2.1]-heptadiene-2,3-diester (**19**) and (**20**) are readily isomerized to the aminophthalate esters (**60**) and (**61**).¹⁶ An alternative structure (**62**) for the product from **20** has not been specifically excluded (see Section III, F), but structure **61** is suggested¹⁶ on analogy with the migration of a methyl group from the bridgehead position accompanying ring opening of the 7-oxabicyclo[2.2.1]heptadienes **63** and **64** in trifluoroacetic acid, which gives the products **65** and **66**, respectively.²⁸ The diacid corresponding

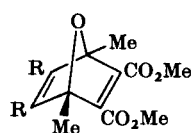


(60) R = H

(61) R = Me

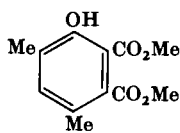


(62)

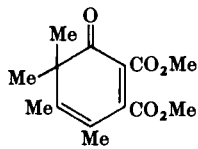


(63) R = H

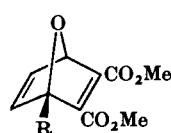
(64) R = Me



(65)



(66)



(67) R = MeO

(68) R = *p*-MeOC₆H₄

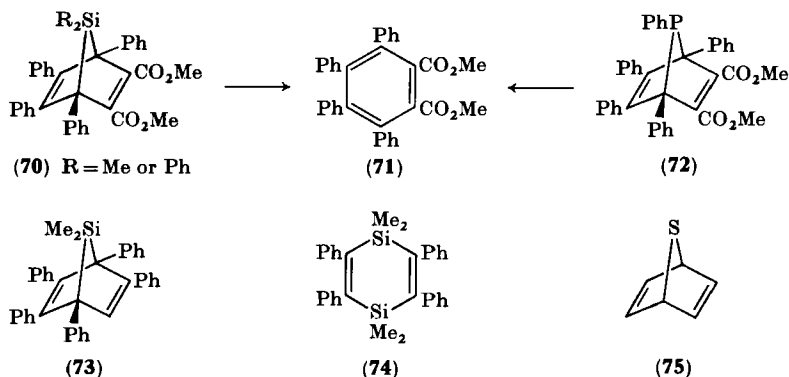
(69) R = H

to **63** isomerizes similarly simply on heating.²⁸ The rate-determining step for these rearrangements involves C-N or C-O bond heterolysis to give a ring-opened carbonium ion intermediate (see Sections III, F and IV, C), as indicated by the much milder conditions of acid catalysis required to aromatize the compounds **67** and **68** containing electron-releasing substituents at a bridgehead position.^{28, 38} Conversely, when both bridgehead positions are unsubstituted, as in **69** and **11**, the aromatization is less easily accomplished; in fact, compound **69** in hot trifluoroacetic acid undergoes a retro-Diels-Alder reaction in preference

³⁸ D. C. Ayres and J. R. Smith, *Chem. Commun.*, 886 (1967); A. C. Day and C. G. Scales, *ibid.*, 1228 (1970).

to isomerization.²⁸ The *N*-benzylamino diacid (**5**) is soluble in dilute mineral acid, from which it is recoverable unchanged.⁷

In the 7-azabicyclo[2.2.1]heptadiene series there is as yet no instance known of aromatization by deamination such as occurs with some naphthalen-1,4-imine and anthracen-9,10-imine derivatives (see Sections III, H and IV, D). On the other hand, a close parallel exists between those reactions and some instances of aromatization of bicyclo[2.2.1] structures by loss of a heavier heteroatom from the 7-position, e.g., **70** → **71**.³⁹ 1,2,3,4,5-Pentaphenylphosphole reacts with dimethyl acetylenedicarboxylate at 150° to give the tetraphenylphthalate ester (**71**), which is presumably formed by decomposition of the intermediate 7-phosphabicyclo[2.2.1]heptadiene adduct (**72**),⁴⁰ although no complementary phosphorus-containing product was noted. The 7-silabicyclo[2.2.1]heptadiene (**73**) with diphenylacetylene at 300° afforded pentaphenylbenzene and the 1,4-disilacyclohexa-2,5-diene derivative (**74**).³⁹



Also, treatment of 2,5-dichloro-7-thiabicyclo[2.2.1]heptane with various bases gave benzene, possibly via aromatization of the intermediate 7-thiabicyclo[2.2.1]heptadiene (**75**).⁴¹

F. PHOTOCHEMISTRY

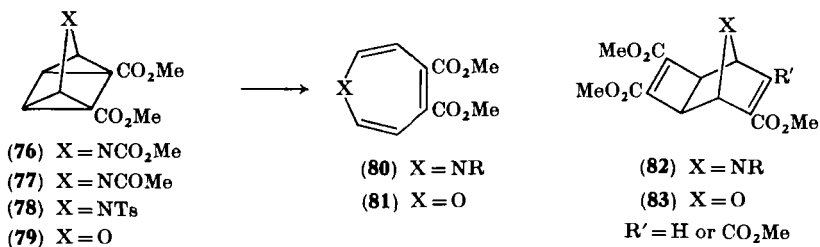
The photochemical valence isomerization of the compounds **11**, **12**, and **14** to the 7-azaquadricyclane derivatives **76–78** is accomplished by

³⁹ H. Gilman, S. G. Cottis, and W. H. Atwell, *J. Amer. Chem. Soc.* **86**, 1596, 5584 (1964).

⁴⁰ E. H. Braye, W. Hübel, and I. Caplier, *J. Amer. Chem. Soc.* **83**, 4406 (1961); cf. also I. G. M. Campbell, R. C. Cookson, and M. B. Hocking, *Chem. Ind. (London)*, 359 (1962).

⁴¹ T. J. Barton, M. D. Martz, and R. G. Zika, *J. Org. Chem.* **37**, 552 (1972).

irradiation in the longest-wavelength UV absorption band.^{15, 42} This exactly parallels the photoisomerization of 7-oxabicyclo[2.2.1]heptadiene derivatives to oxaquadricyclanes,⁴³⁻⁴⁵ e.g., **69** → **79** and of norbornadiene derivatives to quadricyclanes.^{46, 47}



The 7-azaquadricyclane (**77**), like its precursor (**12**), shows evidence in the NMR spectrum of restricted rotation about the N-CO bond.⁴² All the 7-heteroquadricyclanes, **76-79**, are thermolabile,^{15, 42, 43} and they rearrange very readily to the corresponding azepines (**80**) or oxepin (**81**). (In another instance the 7-oxabicyclo[4.1.0] valence-bond tautomer was obtained instead.⁴⁶) In appropriate conditions the addition of acetylenic esters (methyl propiolate and dimethyl acetylenedicarboxylate) competes successfully with the isomerization and gives the *exo*-tricyclic adducts **82** or **83**.⁴⁸⁻⁵⁰

G. ADDITION AND CYCLOADDITION REACTIONS

The stereochemistry of addition of a variety of electrophilic reagents to 7-oxabicyclo[2.2.1]heptadiene derivatives has been described in a

⁴² H. Prinzbach, R. Fuchs, and R. Kitzing, *Angew. Chem. Int. Ed. Engl.* **7**, 67 (1968).

⁴³ H. Prinzbach, M. Argüelles, and E. Druckrey, *Angew. Chem. Int. Ed. Engl.* **5**, 1039 (1966).

⁴⁴ E. Payo, L. Cortés, J. Mantecón, C. Rivas, and G. de Pinto, *Tetrahedron Lett.*, 2415 (1967).

⁴⁵ H. Prinzbach and P. Vogel, *Helv. Chim. Acta* **52**, 396 (1969).

⁴⁶ S. J. Cristol and R. L. Snell, *J. Amer. Chem. Soc.* **80**, 1950 (1958).

⁴⁷ W. G. Dauben and R. L. Cargill, *Tetrahedron* **15**, 197 (1961).

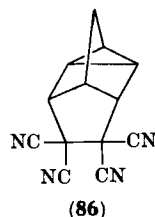
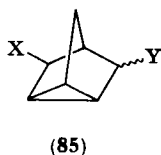
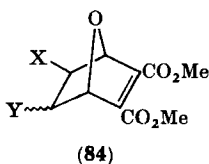
⁴⁸ H. Prinzbach, M. Argüelles, P. Vogel and W. Eberbach, *Angew. Chem. Int. Ed. Engl.* **6**, 1070 (1967).

⁴⁹ W. Eberbach, M. Perroud-Argüelles, H. Achenbach, E. Druckrey, and H. Prinzbach, *Helv. Chim. Acta* **54**, 2579 (1971).

⁵⁰ H. Prinzbach, R. Fuchs, R. Kitzing, and H. Achenbach, *Angew. Chem. Int. Ed. Engl.* **7**, 727 (1968).

series of papers by Russian workers,⁵¹⁻⁵³ addition occurs preferentially to the unsubstituted double bond of the diene (**69**) with formation of cis, exo, and trans adducts (**84**). Cycloaddition of diazomethane or phenyl azide occurs to the remaining double bond in structure **84**,⁵¹⁻⁵³ presumably on the exo side as in similar additions to norbornene and norbornadiene.⁵⁴

Norbornadiene is also known to add electrophilic or free-radical reagents across the 2- and 6-positions with formation of nortricyclene derivatives (**85**).⁵⁵⁻⁵⁸ Neither type of adduct, **84** nor **85**, has yet been obtained from 7-azabicyclo[2.2.1]heptadiene derivatives, but aromatization of the latter is induced by some electrophilic reagents (see Section II, E).



Norbornadiene adds typical dienophiles in a homo-Diels-Alder reaction whereby, for example, the adduct **86** is obtained with tetracyanoethylene.⁵⁹ Dimethyl acetylenedicarboxylate and dicyanoacetylene add to barrelene (bicyclo[2.2.2]octa-2,5,7-triene) in a similar way.⁶⁰

⁵¹ N. S. Zefirov, L. P. Prikazchikova, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **35**, 639 (1965); *Chem. Abstr.* **63**, 4324a (1965).

⁵² N. S. Zefirov, A. F. Davydova, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **34**, 1681 (1964), **35**, 814 (1965), and later references; *Chem. Abstr.* **61**, 5590f (1964), **63**, 9913c (1965).

⁵³ N. S. Zefirov, A. F. Davydova, F. A. Abdulvaleeva, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **36**, 197 (1966); *Chem. Abstr.* **64**, 15865h (1966).

⁵⁴ R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szemies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965), and references cited therein.

⁵⁵ L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.* **78**, 2819 (1956).

⁵⁶ S. Winstein and M. Shatavsky, *Chem. Ind. (London)*, 56 (1956).

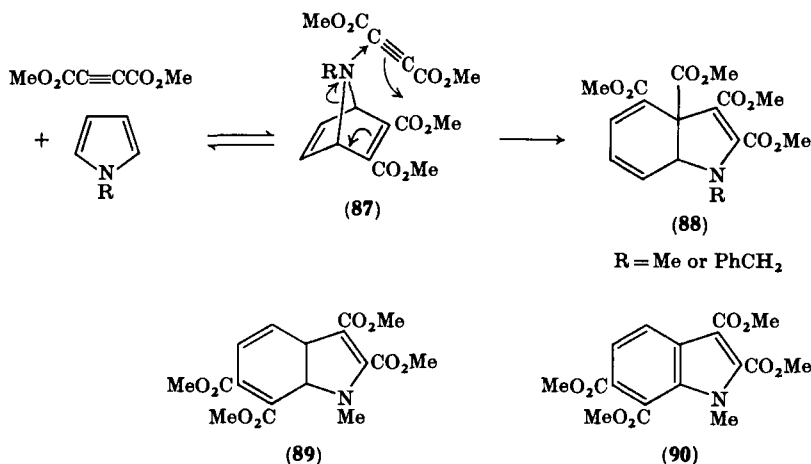
⁵⁷ S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.* **80**, 635 (1958); D. J. Trecker and J. P. Henry, *ibid.* **85**, 3204 (1963).

⁵⁸ For a useful bibliography of additions to norbornadiene see footnote 12 in H. G. Kuivila and C. R. Warner, *J. Org. Chem.* **29**, 2845 (1964); cf. also Shell Chem. Corp. advertisement, *Chem. Eng. News* **35** (7), 23 (1957).

⁵⁹ A. T. Blomquist and Y. C. Meinwald, *J. Amer. Chem. Soc.* **81**, 667 (1959).

⁶⁰ H. W. Zimmerman and G. L. Grunewald, *J. Amer. Chem. Soc.* **86**, 1434 (1964).

A different mode of cycloaddition occurs with 7-azabicyclo[2.2.1]-heptadiene derivatives, in which the nucleophilicity of the nitrogen atom determines the point of attachment of the electrophilic dienophile. The addition depicted in **87**, which may occur in two steps via a zwitterionic intermediate rather than by a concerted mechanism, accounts for the structures (**88**) of 1:2 adducts obtained with *N*-methyl- or *N*-benzylpyrrole and dimethyl acetylenedicarboxylate.⁶¹ At a higher temperature the reaction with *N*-methylpyrrole also afforded the indole tetraester



(**90**) via addition of a second molecule of the acetylenic ester to the intermediate 7-azabicyclo[2.2.1]heptadiene in an alternative sense and aromatization of the resulting dihydroindole (**89**). Although 7-azabicyclo[2.2.1]heptadienes were not isolable from these reactions,^{9, 61} their role as intermediates is amply confirmed by other work (see Section III, G).

III. Naphthalen-1,4-imines

A. SYNTHESSES

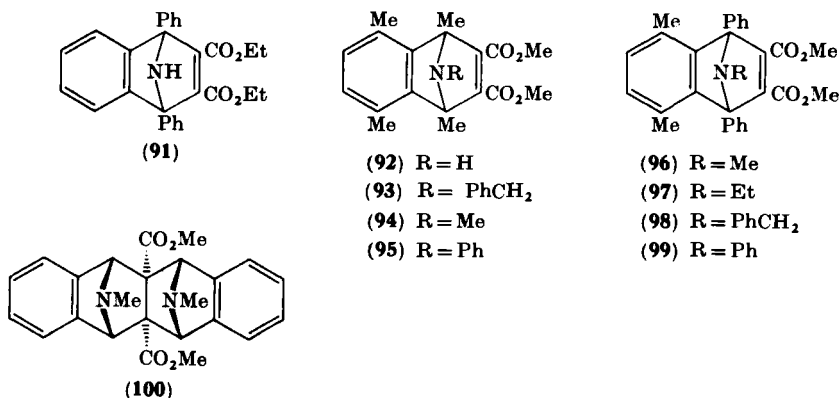
Derivatives of the naphthalen-1,4-imine ring system (**2**) have become available only since the discovery of cycloaddition reactions of benzyne, on the one hand, and the recent rapid development of isoindole chemistry⁶² on the other.

⁶¹ R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

⁶² J. D. White and M. E. Mann, *Advan. Heterocycl. Chem.* **10**, 113 (1969), and references therein.

1. 1,4-Dihydronaphthalen-1,4-imines from Isoindoles

The naphthalen-1,4-imine derivatives **91–99** have been obtained by addition of acetylenedicarboxylic esters to the appropriate isoindoles.^{63–65} Some such adducts react further with acetylenic esters (see Sections III, G and H), so that *N*-ethyl- and *N*-*n*-butylisoindole give 1:2 adducts with dimethyl acetylenedicarboxylate instead.⁶⁵ *N*-Methylisoindole appears to be exceptional in giving an oily 2:1 adduct, for which structure (**100**) was suggested⁶⁶ on analogy with the 2:1 adduct obtained from 1,3-diphenylbenz[*c*]furan and acetylenedicarboxylic acid.⁶⁷



The reactions of isoindoles with other acetylenic dienophiles have yet to be explored.

2. 1,4-Dihydronaphthalen-1,4-imines from Pyrroles

Although pyrrole itself and benzyne afford 2-phenylpyrrole,⁶⁸ the Diels–Alder addition of benzyne to substituted pyrroles provides an alternative synthesis of naphthalen-1,4-imines^{68–74} (see Table II).

⁶³ J. C. Emmett and W. Lwowski, *Tetrahedron* **22**, 1011 (1966).

⁶⁴ C. O. Bender, R. Bonnett, and R. G. Smith, *J. Chem. Soc. C*, 1251 (1970).

⁶⁵ L. J. Kricka and J. M. Vernon, *J. Chem. Soc. Perkin Trans. 1*, 904 (1972).

⁶⁶ G. Wittig and H. Ludwig, *Ann.* **589**, 55 (1954).

⁶⁷ J. A. Berson, *J. Amer. Chem. Soc.* **75**, 1240 (1953).

⁶⁸ G. Wittig and B. Reichel, *Chem. Ber.* **96**, 2851 (1963).

⁶⁹ G. Wittig and W. Behnisch, *Chem. Ber.* **91**, 2358 (1958).

⁷⁰ L. A. Carpino and D. E. Barr, *J. Org. Chem.* **31**, 764 (1966).

⁷¹ G. Kaupp, J. Perreten, R. Leute, and H. Prinzbach, *Chem. Ber.* **103**, 2288 (1970).

⁷² D. D. Callander, P. L. Coe, J. C. Tatlow, and A. J. Uff, *Tetrahedron* **25**, 25 (1969).

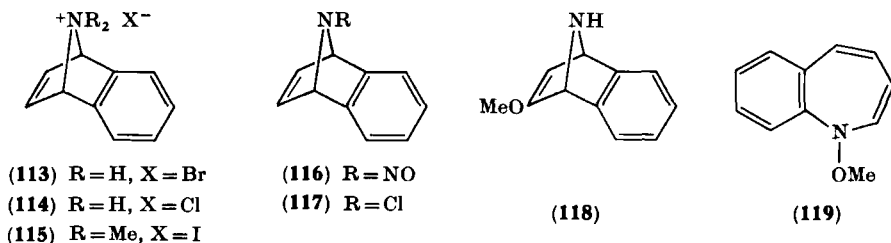
⁷³ G. W. Gribble, N. R. Easton, and J. T. Eaton, *Tetrahedron Lett.*, 1075 (1970).

⁷⁴ E. Wolthuis and A. De Boer, *J. Org. Chem.* **30**, 3255 (1965); E. Wolthuis, W. Cady, R. Roon, and B. Weidenaar, *ibid.* **31**, 2009 (1966).

TABLE II
1,4-DIHYDRONAPHTHALEN-1,4-IMINES FROM PYRROLES

Structure	Substituents	Yield (%)	References
(2)	None	6 as (113)	68
(101)	<i>N</i> -Me	7 as (115)	69
(102)	<i>N</i> -CH ₂ Ph	14 as picrate	68
(103)	<i>N</i> -CO ₂ - <i>t</i> -Bu	35-41	70
(104)	<i>N</i> -CO ₂ Me	65	71
(105)	<i>N</i> -Ts	49	71
(106)	2,3, <i>N</i> -(CO ₂ Me) ₃	55	71
(107)	5,6,7,8-F ₄ - <i>N</i> -Me	52	72
(108)	5,6,7,8-Cl ₄ - <i>N</i> -Me	—	73
(109)	1,2,3,4-Me ₄ - <i>N</i> -CH ₂ Ph	50	74
(110)	1,2,3,4-Me ₄ - <i>N</i> -Ph	51	74
(111)	1,2,3,4-Me ₄ - <i>N</i> - <i>n</i> -Bu	63	74
(112)	1,2,3,4-Me ₄ - <i>N</i> -cyclo-C ₆ H ₁₁	59	74

It should be noted that the 1:1 adducts of benzyne with pyrrolylmagnesium iodide, and *N*-methyl- and *N*-benzylpyrrole were isolated and characterized only as the hydrobromide (113), the methiodide (115), and the picrate of 102, respectively. The low yields of all these derivatives are due in part to further reactions of the naphthalen-1,4-imines with benzyne (see Section III, F and G). Yields are better where the starting pyrrole has an electron-withdrawing N-substituent. Some analogous naphthalen-1,4-imines expected from 1,2,5-trisubstituted pyrroles apparently rearrange spontaneously to β -naphthylamine derivatives under the conditions for their formation (see Section III, F). The related adducts 107 and 108 are formed from tetrahalobenzyne and *N*-methylpyrrole.



3. Substitutions at the Nitrogen Atom

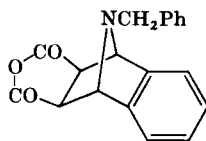
Treatment of the *t*-butyl ester (103) with dry hydrogen chloride in cold nitromethane gave the hydrochloride (114), from which the free

base (**2**) was liberated with alkali.⁷⁰ The reverse transformation of **2** → **103** was achieved with *t*-butyl azidoformate in pyridine, and the nitrosamine (**116**) and chloramine (**117**) have been obtained from **2** with nitrosyl chloride and *N*-chlorosuccinimide, respectively.^{70, 75}

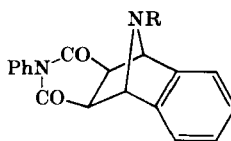
Methanolysis of the syn isomer of **117** (see Section III,B) is anchimerically assisted and gives the rearranged ether (**118**).⁷⁵ Silver ion-assisted methanolysis of *anti*-**117** is also attended by rearrangement; the product is formulated as the 1-benzazepine (**119**). Mechanisms are suggested for both of these rearrangements.⁷⁵

4. 1,2,3,4-Tetrahydronaphthalen-1,4-imines from Isoindoles

Whereas pyrroles react, if at all, with maleic anhydride to give Michael adducts via electrophilic substitution in the pyrrole ring,⁷⁶ isoindoles more often give Diels–Alder adducts with maleic acid derivatives; these contain the 1,2,3,4-tetrahydronaphthalen-1,4-imine ring system. The formation of such adducts has been widely used for trapping and characterization of labile isoindoles,^{62–64, 66, 77–81} although some of the adducts are known to dissociate in solution and/or to rearrange to the isomeric Michael adducts.^{63, 64} Endo stereochemistry has sometimes been assumed for the Diels–Alder adducts, probably incorrectly; e.g., in the adduct (**120**) of *N*-benzylisoindole and maleic anhydride the singlet NMR absorption⁸⁰ for the hydrogen atoms at C-2 and C-3 demonstrates exo orientation of the anhydride. Both endo and exo adducts are obtained⁷⁹ from *N*-*p*-tolylisoindole and *N*-phenylmaleimide and in some other cases.^{64, 81} The *N*-phenylmaleimide adduct (**121**) of isoindole itself



(120)



(121) R = H

(122) R = MeCO

⁷⁵ V. Rautenstrauch, *Chem. Commun.*, 1122 (1969).

⁷⁶ O. Diels, K. Alder, and D. Winter, *Ann.* **486**, 211 (1931).

⁷⁷ G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Ann.* **572**, 1 (1951); G. Wittig and H. Streib, *ibid.* **584**, 1 (1953); G. Wittig, G. Closs, and F. Mindermann, *ibid.* **594**, 89 (1955).

⁷⁸ W. Theilacker and W. Schmidt, *Ann* **597**, 95 (1955).

⁷⁹ R. Kreher and J. Seubert, *Z. Naturforsch. B* **20**, 75 (1965); *Angew. Chem. Int. Ed. Engl.* **5**, 967 (1966).

⁸⁰ G. Cignarella and G. G. Giorgio, *Gazz. Chim. Ital.* **99**, 1115 (1969).

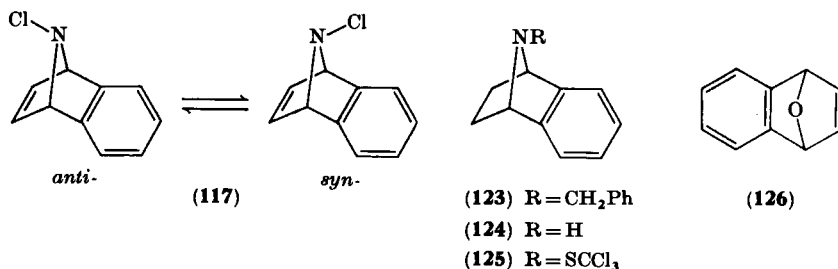
⁸¹ R. Bonnett and R. F. C. Brown, *Chem. Commun.*, 393 (1972).

can be converted to the *N'*-acetyl derivative (122),⁷⁹ in contrast to the behavior of the tetraester derived from 51, which is apparently too hindered.²⁴

B. CONFIGURATIONAL CHANGES AT THE NITROGEN ATOM

Preliminary studies of nitrogen substituent inversion processes have been reported for several naphthalen-1,4-imine derivatives. The syn and anti invertomers of the *N*-chloroamine (117) equilibrate in solution to a mixture in proportion $\sim 3:2$. The process can be followed kinetically by NMR spectroscopy starting from the pure anti compound;⁷⁵ the inversion is relatively slow ($k_1 = 2.5 \times 10^{-5} \text{ sec}^{-1}$ at 23°), and the free-energy barrier to inversion is as high ($\Delta F^\ddagger = 23.5 \text{ kcal mole}^{-1}$) as values found for inversion in aziridines.³³ (*N*-Chloroaziridine derivatives, for which the energy barrier is even higher,⁸² have also been resolved into diastereoisomeric invertomers.^{83, 84})

For the *N*-methyl compounds 107 and 108 the syn \rightleftharpoons anti inversion is faster ($\Delta F^\ddagger = \sim 14 \text{ kcal mole}^{-1}$);⁷³ the NMR spectrum of each compound at 22° consists of three time-averaged signals for the vinylic, bridgehead, and *N*-methyl hydrogen atoms, each of which broadens and splits into two as the temperature is lowered. The major component of the mixture was tentatively suggested to be the anti invertomer for each of 107 and 108. Similar results were described for the *N*-benzyl derivatives 102 and 123.³⁴



The free-energy barriers for rotation about the N-CO bond in the *N*-acetyl and *N*-benzoyl derivatives of 2 and 124 have been calculated³⁴ from the coalescence temperature for the NMR signals for the bridge-

⁸² J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

⁸³ S. J. Brois, *J. Amer. Chem. Soc.* **90**, 508 (1968).

⁸⁴ D. Felix and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **7**, 224 (1968).

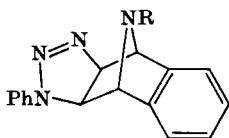
head hydrogen atoms to lie between 15 and 18 kcal mole⁻¹. Restricted rotation is also evident from the NMR spectrum of the trichloromethyl-sulfenamide (**125**).³⁴

C. ADDITIONS TO THE 2,3-DOUBLE BOND

Several 1,2,3,4-tetrahydronaphthalen-1,4-imines have been prepared by catalytic hydrogenation,^{70,71} e.g., **2** → **124**. Compound **109** was similarly reduced to a dihydro derivative,⁷⁴ although the product in this case was characterized only by its UV absorption spectrum, which was very similar to that of **109** except for the absence of the absorption maximum at longest wavelength (282 nm, log ϵ 2.9). The UV spectra of both **109** and its dihydro derivative exhibited small reversible hypsochromic shifts on addition of acid.⁷⁴

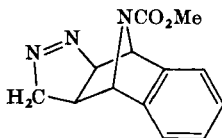
Protonic acids and some other electrophiles cause the aromatization of naphthalen-1,4-imines and of derivatives of the related 1,4-epoxy-1,4-dihydronaphthalene ring system (**126**) to naphthalene derivatives (see Section III, F), and simple electrophilic addition to the 2,3-double bond has not been observed. Ring-opening of the ether (**126**) also occurs on addition of alkyl or aryl lithium reagents as a result of exo attack by the nucleophile at the 2-position.^{69, 85, 86}

When 1,4-dihydronaphthalen-1,4-imine (**2**) was first obtained via the hydrobromide (**113**), it was shown to react with phenyl azide to give an adduct (**127**).⁶⁸ The analogous phenyl azide adduct (**128**) from compound **103** has been better characterized.⁷⁰ Naphthalen-1,4-imines also add diazomethane across the 2,3-double bond, forming pyrazolines, e.g., **104** → **129**, two of which have been photolyzed to give the corresponding cyclopropane derivatives (**130**) with extrusion of nitrogen.⁷¹

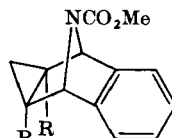


(**127**) R = H

(**128**) R = CO₂-*t*-Bu



(**129**)



(**130**)

R = H or CO₂Me

The exo stereochemistry of compounds **127**–**130**, although not unambiguously clear from their NMR spectra (where these have been recorded),

⁸⁵ R. Caple, G. M.-S. Chen, and J. D. Nelson, *J. Org. Chem.* **36**, 2874 (1971).

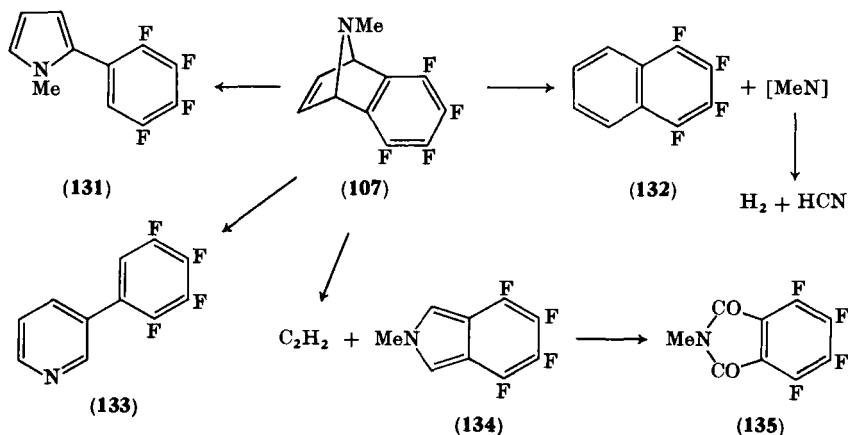
⁸⁶ G. Wittig and L. Pohmer, *Angew. Chem.* **67**, 348 (1955); *Chem. Ber.* **89**, 1334 (1956).

is very probable on analogy with similar additions to norbornene.⁵⁴ Cycloadditions of diazomethane, phenyl azide,⁸⁶ and of various 1,3-dienes^{87, 88} to the 2,3-double bond of 1,4-epoxy-1,4-dihydronaphthalene (**126**) have been described. The addition of chlorocyanoacetylene and of 4-phenyl-1,2,4-triazolin-3,5-dione to compound **126** gives rearranged products, to which structures have been assigned so far only on the evidence of NMR spectra.⁸⁹

D. THERMAL STABILITY

With one exception,⁹⁰ naphthalen-1,4-imines with a double bond between C-2 and C-3 are not known to dissociate thermally by either possible retro-Diels-Alder pathway (the reverse of reactions described in Section III, A, 1 and 2), and the enthalpy requirements for the formation of a benzyne or an acyclic acetylene are doubtless unfavorable. However, the mass spectra of compounds **93-99** reveal one important fragmentation of the molecular ions to be loss of dimethyl acetylenedicarboxylate, and another fragmentation pathway involves the formation of nitrilium ions $\text{MeC}\equiv\text{N}^+\text{R}$ and $\text{PhC}\equiv\text{N}^+\text{R}$ from **93-95** and **96-99**, respectively.⁸⁵

The pyrolysis of **107** in solution at 106° results in isomerization to the 1-methyl-2-tetrafluorophenylpyrrole (**131**).⁹⁰ Pyrolysis of **107** in the gas phase at 325° gives a variety of products including acetylene and



⁸⁷ G. Wittig, H. Härle, E. Knauss, and K. Niethammer, *Chem. Ber.* **93**, 951 (1960).

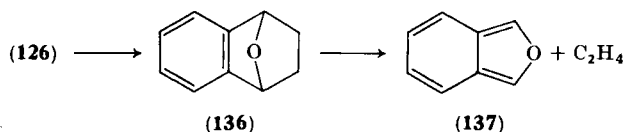
⁸⁸ E. Wolthuis, *J. Org. Chem.* **26**, 2215 (1961).

⁸⁹ T. Sasaki, K. Kanematsu, and M. Uchide, *Tetrahedron Lett.*, 4855 (1971).

⁹⁰ P. L. Coe and A. J. Uff, *Tetrahedron* **27**, 4065 (1971).

N-methyltetrafluorophthalimide (**135**), which is probably formed via autoxidation of the isoindole (**134**); hydrogen cyanide, tetrafluoronaphthalene (**132**), and 3-tetrafluorophenylpyridine (**133**) are also obtained, and mechanisms are suggested to account for their formation.⁹⁰

1,2,3,4-Tetrahydronaphthalen-1,4-imines are very much more labile to thermal decomposition. Diels-Alder addition of maleic anhydride to isoindoles is easily reversible (see Section III,A, 4), and the phenyl azide adducts **127** and **128** give 1-phenyl-1,2,3-triazole on pyrolysis,^{68, 70} although the corresponding isoindoles were not detected. The analogous flash pyrolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**136**) has afforded a preparative route to the unsubstituted benz[*c*]furan (**137**).^{91, 91a}



E. PHOTOCHEMISTRY

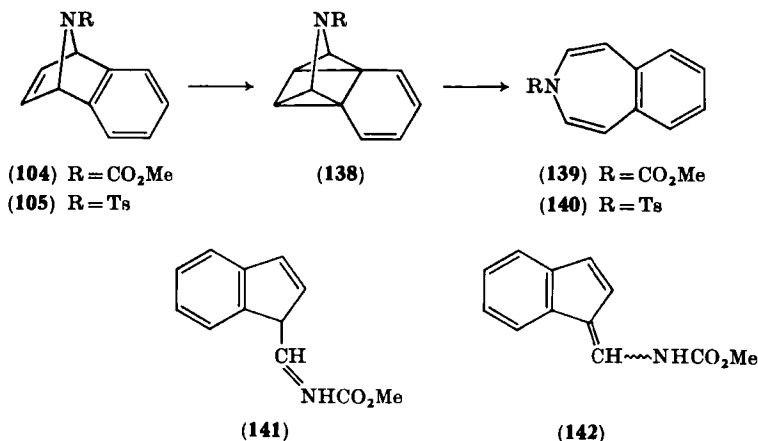
UV irradiation of the naphthalen-1,4-imines **104** and **105** promotes their isomerization to 3-benzazepine derivatives **139** and **140**.⁷¹ Although no direct evidence was obtained to confirm the formation of azaquadricyclanes (**138**) as intermediates (see Section II,F), the extra strain associated with structure **138** and the extra benzenoid stabilization of the products **139** and **140** make it understandable that the thermal rearrangement of **138** should occur faster than that of **76** or **78**. Analogous photochemical transformations are those of compound **106** to trimethyl 3-benzazepin-1,3,5-tricarboxylate,⁷¹ and of 1,4-epoxynaphthalenes to benzoxepin derivatives.⁹²

By-products of the direct excitation of **104** were the isomeric *cis*- and *trans*-benzofulvene derivatives (**142**), which were also obtained as the main products of the triplet-sensitized excitation of **104** in the presence of ketones. Acid-catalyzed prototropic rearrangement of a colorless precursor (**141**) was suggested to account for formation of **142**.⁷¹

⁹¹ U. E. Wiersum and W. J. Mijs, *Chem. Commun.*, 347 (1972).

^{91a} *Added in Proof*: Isoindole and ethylene are similarly obtained by vacuum pyrolysis of **124**; see J. Bornstein, D. E. Remy, and J. E. Shields, *Chem. Commun.*, 1149 (1972). The 2,3-dihydro derivative of adduct (**107**) also gives the corresponding isoindole at only 120°; see H. Heaney, S. V. Ley, A. P. Price, and R. P. Sharma, *Tetrahedron Lett.*, 3067 (1972).

⁹² G. R. Ziegler and G. S. Hammond, *J. Amer. Chem. Soc.* **90**, 513 (1968); G. R. Ziegler, *ibid.* **91**, 446 (1969).

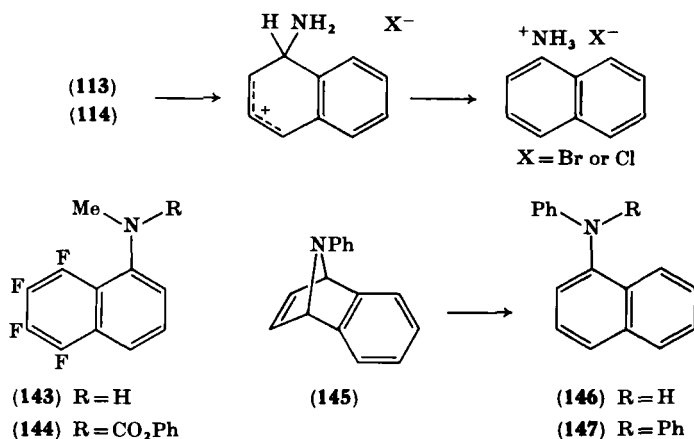


F. AROMATIZATION

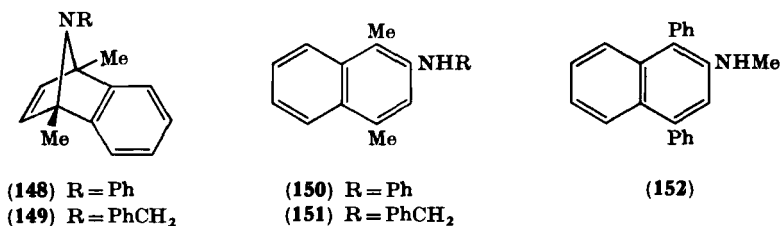
The hydrobromide (113) and the hydrochloride (114) of 1,4-dihydronaphthalen-1,4-imine (2) rearrange at their melting points to give α -naphthylamine hydrobromide⁶⁸ and hydrochloride,⁷⁰ respectively. The aromatization of (114) was also observed to occur in solution at room temperature.⁷⁰ These reactions are analogous to the acid-catalyzed isomerization of 1,4-epoxynaphthalene (126) to α -naphthol.⁸⁶ The *N*-methyl compound (107) was similarly converted to the isomeric α -naphthylamine derivative (143) with hydrochloric acid,⁷² and the methiodide (115) was aromatized to *N,N*-dimethyl- α -naphthylamine in methanol in the presence of moist silver oxide.⁶⁹ The *N*-benzyl-naphthalen-1,4-imine (102) on attempted distillation gave *N*-benzyl- α -naphthylamine,⁶⁸ and the analogous *N*-phenyl compound (145) is apparently even more labile, since it was not isolated but gave the naphthylamine (146) and other products (see below and Section III, G) under the conditions used for addition of benzyne to *N*-phenylpyrrole.⁶⁸ (This difference is plausibly a consequence of the phenyl group being more electron-withdrawing than benzyl.)

Similar aromatizations of naphthalen-1,4-imines can be brought about by other electrophilic reagents, the end result being the formation of *N*-substituted α -naphthylamines. For example, the intermediate 145 is also attacked by benzyne to give *N,N*-diphenyl- α -naphthylamine (147)⁶⁸ (see also Section III, G). The reaction of 107 with phenyl chloroformate to give the *N*- α -naphthyl carbamate (144) is analogous.⁷²

Surprisingly, in view of the preparation of 1,2,3,4-*N*-penta-substituted naphthalen-1,4-imines (109–112),⁷⁴ the 1,4-*N*-trisubstituted compounds



148 and **149** to be expected from addition of benzyne to the corresponding 1,2,5-trisubstituted pyrroles could not be isolated;⁹³ they rearranged under the conditions of the reaction (possibly due to electrophilic catalysis by magnesium halides) to the β -naphthylamine derivatives (**150** and **151**). The product obtained from benzyne and 1-methyl-2,5-

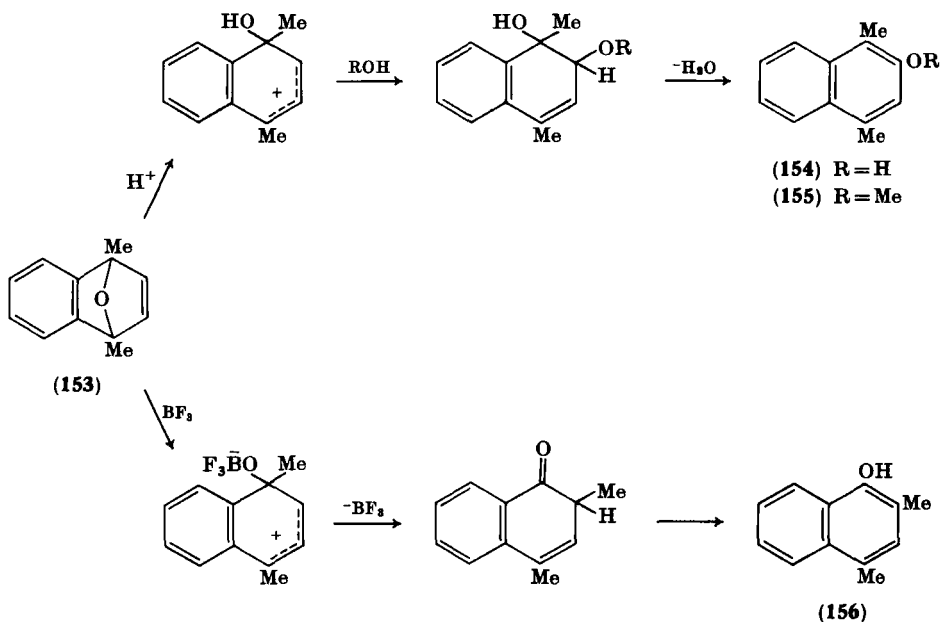


diphenylpyrrole was similarly the rearranged adduct (**152**).⁹³ The formal analogy to the acid-catalyzed isomerization of 1,4-epoxy-1,4-dihydro-1,4-dimethylnaphthalene (**153**) to the β -naphthol (**154**) is deceptive, since in the latter case the hydroxyl group in **154** has been shown to be derived from solvent water.⁹⁴ Also, the main product from aromatization of **153** in methanolic hydrochloric acid is the methyl ether (**155**),⁹⁵ which is formed not via the naphthol (**154**) but probably via addition of methanol to an intermediate carbonium ion, as shown in Scheme 1.

⁹³ E. Wolthuis, D. V. Jagt, S. Mels, and A. De Boer, *J. Org. Chem.* **30**, 190 (1965).

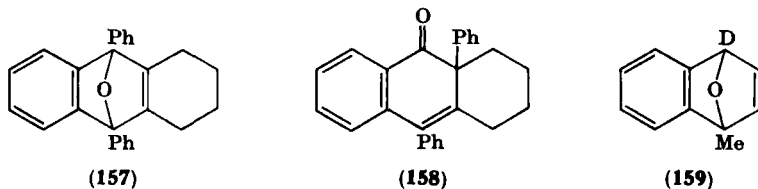
⁹⁴ M. Fetizon and N. T. Anh, *Bull. Soc. Chim. Fr.*, 3208 (1965).

⁹⁵ E. Wolthuis, B. Bossenbroek, G. DeWall, E. Geels, and A. Leegwater, *J. Org. Chem.* **28**, 148 (1963).



SCHEME 1

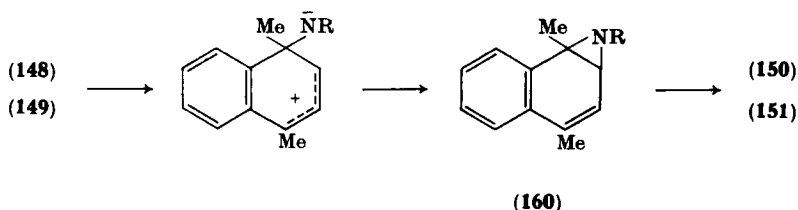
In nonnucleophilic conditions (catalysis by boron trifluoride in dry benzene) the carbonium ion intermediate is longer-lived and aromatization of **153** is then accompanied by migration of a methyl group to give the α -naphthol (**156**) isomeric with **154**.⁹⁴ This result is analogous to the aromatizations of 7-oxabicyclo[2.2.1]heptadiene derivatives²⁸ already described (see Section II, E). A similar migration of a phenyl group (**157** \rightarrow **158**) occurs in hot acetic acid,⁹⁶ and the cyclohexadienone (**158**) in this case cannot tautomerize to a naphthol. The deuterium-labeled ether (**159**) is aromatized by acid to 4-methyl-1-naphthol with partial retention of deuterium at its 2-position.⁹⁷



⁹⁶ G. Wittig and U. Mayer, *Chem. Ber.* **96**, 329 (1963).

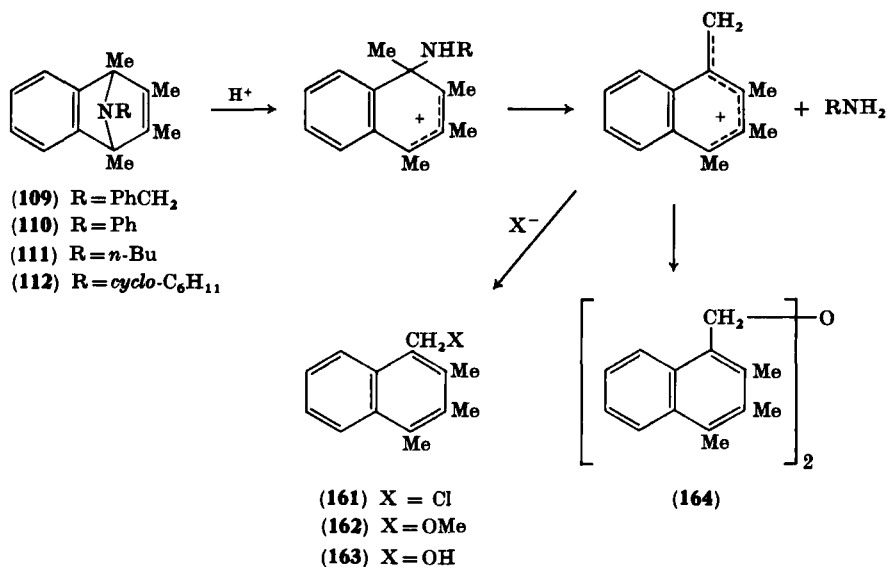
⁹⁷ J. V. Bardouille and J. M. Vernon, unpublished results.

Aromatization of 5,8-di-*t*-butyl-1,4-epoxy-1,4-dihydronaphthalene with ethanolic hydrogen chloride gives a β -chloronaphthalene as well as an α -naphthol, especially when deuterium rather than protium has to be lost from the 1- or 4-position; this result has been interpreted in terms of a compression effect between substituents at the 1- and 8-positions.⁹⁸ For the formation of the β -naphthylamines **150**–**152**, the structures of which are proved beyond reasonable doubt,⁹³ it is the internal (nitrogen) nucleophile which appears at the 2-position in the isolated product. Possibly ring-opening of the expected naphthalen-1,4-imine (**148** and **149**) gives first a zwitterion which collapses to an aziridine intermediate (**160**), from which the β -naphthylamine is derived via a second rearrangement. It is surprising, though, that the rearrangement occurred under conditions of reaction and work-up which preclude acid catalysis other than by magnesium halides.



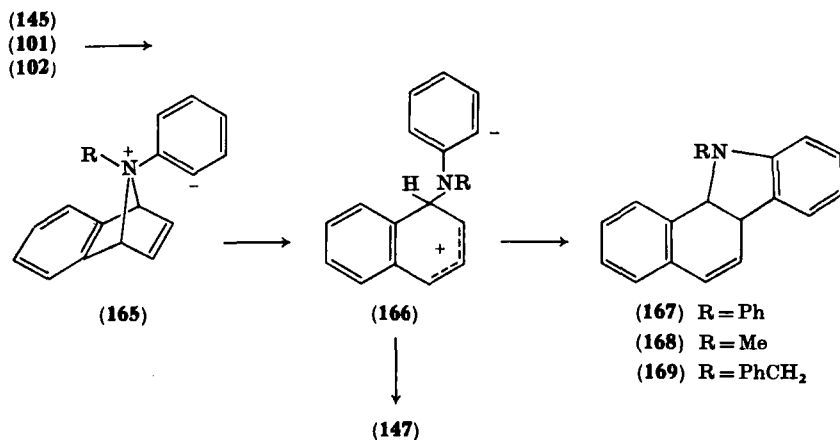
The acid-catalyzed aromatization of 1,2,3,4-tetramethylnaphthalen-1,4-imines (**109**–**112**) is accomplished only by deamination and incorporation of a substituent (derived from external nucleophile) into an α -methyl group. Thus, dry hydrogen chloride converts the *N*-benzyl compound **109** into **161**, methanolic hydrogen chloride gives instead the α -naphthylmethyl ether (**162**), whereas in hot aqueous hydrochloric acid the bis(α -naphthylmethyl) ether (**164**) is the main product;⁷⁴ benzylamine was also obtained from two of these reactions. The ether (**164**) also results from **110**–**112** in hot hydrochloric acid, but the use of cold very dilute acid gives the corresponding alcohol (**163**) instead.⁷⁴ Compounds **161** and **162** are likewise obtainable from 1,4-epoxy-1,4-dihydro-1,2,3,4-tetramethylnaphthalene with hydrogen chloride under appropriate conditions.⁹⁵ Migration of a bridgehead methyl group has not been recorded in this series of compounds.

⁹⁸ R. W. Franck and K. Yanagi, *Tetrahedron Lett.*, 1789 (1967); *J. Org. Chem.* **33**, 811 (1968).



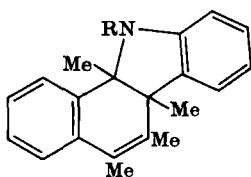
G. CYCLOADDITIONS INVOLVING THE NITROGEN ATOM

The major product (21–37%) from the reaction of benzyne with *N*-phenylpyrrole is the 2:1 adduct (167),⁶⁸ the formation of which is explicable in terms of the cyclization of either one of two intermediate zwitterions, 165 or 166. Alternatively, prototropic shift within the intermediate (166) accounts for the formation of the α -naphthylamine (147) (4–6% yield). Other benz[*a*]carbazole derivatives (168 and 169)

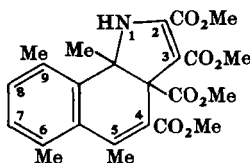


were obtained alongside the 1:1 adducts (**101** and **102**) of benzyne and *N*-alkylpyrroles.^{68, 69} Some analogous adducts (**170–172**) with bridgehead substituents result from the reaction of 1,2,3,4-tetramethylnaphthalene-1,4-imines or of pentamethylpyrrole with benzyne.⁷⁴

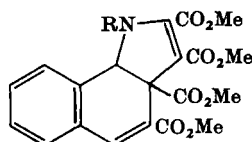
Similar cycloaddition reactions have been described using dimethyl acetylenedicarboxylate. For example, 1,3,4,7-tetramethylisindole reacts stepwise with the acetylenic ester at room temperature, giving the 1:1 adduct (**92**) which with more of the acetylenic ester in refluxing benzene affords the rearranged 1:2 adduct (**173**).⁶⁴ *N*-Ethyl- and *N*-*n*-butylisindole with dimethyl acetylenedicarboxylate at 0° give the corresponding 1:2 adducts (**174** and **175**) as the only isolable products.⁶⁵ Surprisingly, *N*-substituted derivatives of the naphthalen-1,4-imine

(170) R = *n*-Bu(171) R = *cyclo*-C₆H₁₁

(172) R = Me



(173)



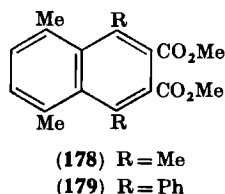
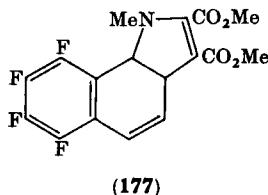
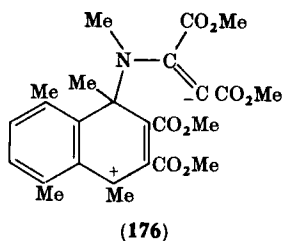
(174) R = Et

(175) R = *n*-Bu

(**92**) either fail to react with dimethyl acetylenedicarboxylate or they react in a different sense to give deaminated products (see Section III, H). The inertness of the *N*-phenyl derivatives (**95** and **99**) is tentatively ascribed⁹⁹ to the reduced nucleophilicity of the nitrogen atom with an electron-withdrawing substituent. The *N*-methyl derivative (**94**) reacts with the acetylenic ester, but an adduct analogous to **173** is not obtained. Dreiding models of 3*a*,9*b*-dihydrobenz[*g*]indoles with a *cis* ring junction, as is likely for the adduct **173**, show steric hindrance between an *N*-substituent and the methyl group at the 9-position. This strain may well prevent cyclization of an intermediate such as zwitterion **176** analogous to **166**. Some support for this hypothesis is found from a study of the reaction of the naphthalen-1,4-imine (**107**) with dimethyl acetylenedicarboxylate, which gives the 1:1 adduct (**177**) and other products.¹⁰⁰ In the NMR spectrum of **177** the signal for the *N*-methyl group appears as a doublet ($J = 3$ Hz), apparently split by the fluorine atom at the 9-position, reflecting the close proximity of the nuclei concerned in that crowded region of the molecule.

⁹⁹ L. J. Kricka and J. M. Vernon, *Chem. Commun.*, 942 (1971); *J. Chem. Soc. Perkin Trans. 1*, 766 (1973).

¹⁰⁰ L. J. Kricka and J. M. Vernon, unpublished work.

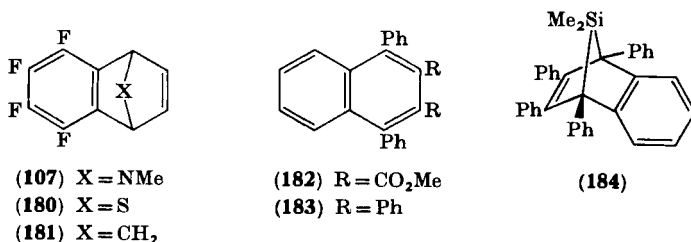


H. DEAMINATION

The formation of a small amount of naphthalene as a by-product of the reaction of benzyne with *N*-methylpyrrole was noted by Wittig and Behnisch.⁹⁹ Some related examples have recently been described.⁹⁹ The tetrachloronaphthalen-1,4-imine (**108**) with benzyne gave *N*-methylcarbazole, which it is tempting to see as arising from the reaction of an intermediate zwitterion (compare **166**) with another molecule of benzyne or, more likely, a benzyne precursor. The complementary product, 1,2,3,4-tetrachloronaphthalene, was not identified in this case.

The 1,4-dihydronaphthalen-1,4-imine-2,3-diester (**94**) on heating with dimethyl acetylenedicarboxylate is deaminated to the naphthalene diester (**178**), in which the same pattern of substitution as that present in **94** was assured by degradation via the cyclic 2,3-dicarboxylic anhydride to 1,4,5,8-tetramethylnaphthalene.⁹⁹ Analogously, compounds **96** and **97** with the acetylenic ester at $\sim 180^\circ$ gave some of the naphthalene (**179**). Bridging *N*-methyl groups are also lost from the naphthalen-1,4-imines **108** and **107** on treatment with dimethyl acetylenedicarboxylate under milder conditions to give tetrachloro- and tetrafluoronaphthalene, respectively [the latter alongside (**177**) and other products].¹⁰⁰ In none of these cases of deamination was a complementary nitrogen-containing product identified. Naphthalen-1,4-imines with *N*-benzyl or *N*-phenyl groups are unreactive to the acetylenic ester.

Direct extrusion of methyl nitrene has been discounted as an explanation of these deamination reactions, which are apparently induced by attack of the acetylenic ester and thus more likely take place via an intermediate analogous to **176**. On the other hand, the products from pyrolysis of **107** at 325° include 1,2,3,4-tetrafluoronaphthalene (**132**) and hydrogen cyanide, and it was suggested⁹⁰ that methyl nitrene was the precursor of the latter compound (see Section III,D). The adduct (**180**) of tetrafluorobenzyne and thiophen extrudes sulfur so readily



that the isolable reaction product is **132**.⁷² 1,3-Diphenylbenz[*c*]-thiophen reacts with dimethyl acetylenedicarboxylate in refluxing xylene to give the 1,4-diphenylnaphthalene-2,3-diester (**182**) by similar loss of sulfur from an intermediate adduct.¹⁰¹ Pyrolysis of the sila-heterocycle **184** at 300° gave 1,2,3,4-tetraphenylnaphthalene (**183**) in high yield. (The dimethylsilylene could be trapped as **74** in the presence of diphenylacetylene.³⁹) Even the carbocyclic adduct (**181**) of tetrafluorobenzynes and cyclopentadiene loses the methylene bridge at 280° to give **132**.⁷² The *N*-nitrosamine (**116**) decomposes smoothly at 45° to give naphthalene and, presumably, nitrous oxide, whereas the *N*-nitroso derivative of **124** is more thermostable, at least to 100°. ⁷⁰

IV. Anthracen-9,10-imines

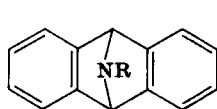
A. SYNTHESSES

Few derivatives of the anthracen-9,10-imine ring system (**3**) are known, the only route for their preparation being the addition of benzyne to isoindoles. *N*-Methyl- and *N*-phenylisoindole with benzyne gave the adducts **185** and **186** (54% and 11%, respectively) together with other products resulting from secondary reactions of benzyne with the 1:1 adducts¹⁰¹ (see Sections IV,C and D). Benzyne generated by three different methods was trapped by addition to 2-methyl-1,3-diphenylisoindole to give the anthracen-9,10-imine (**190**) in 58–75% yield.¹⁰² Compounds **187–191** have been obtained by the same route,^{63, 99} and the 9,10-epoxy- and 9,10-epithioanthracene derivatives (**193** and **194**) result from benzyne additions to related heterocyclic systems.¹⁰¹

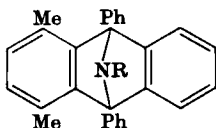
The *N*-ethoxycarbonyl derivative (**192**) was obtained from **191** with ethyl chloroformate and butyllithium, although pyridine, triethylamine,

¹⁰¹ G. Wittig, E. Knauss, and K. Niethammer, *Ann* **630**, 10 (1960).

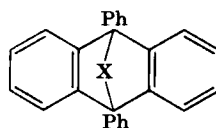
¹⁰² R. Harrison, H. Heaney, and P. Lees, *Tetrahedron* **24**, 4589 (1968).



- (3) R = H
(185) R = Me
(186) R = Ph



- (187) R = Me
(188) R = PhCH₂
(189) R = Ph

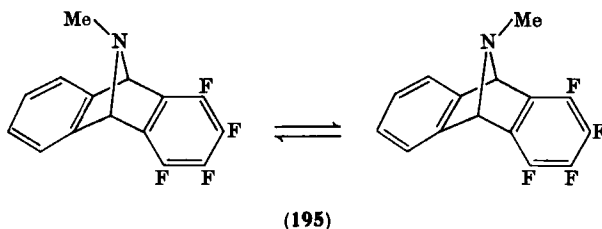


- (190) X = NMe
(191) X = NH
(192) X = NCO₂Et
(193) X = O
(194) X = S

lithium hydride, and potassium carbonate were insufficiently basic to effect this transformation.⁶³

B. CONFIGURATIONAL CHANGES AT THE NITROGEN ATOM

A preliminary study by NMR spectroscopy has been made of the equilibration of N-invertomers for the anthracen-9,10-imine (195).⁷³

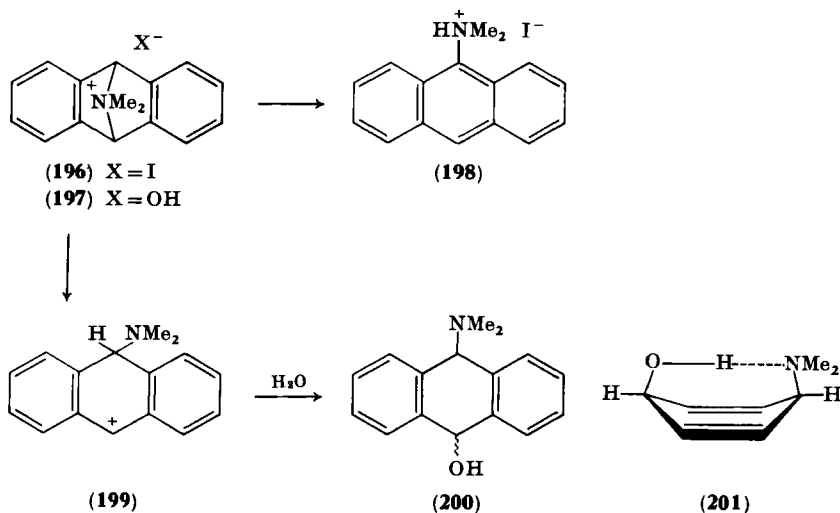


C. RING-OPENING REACTIONS

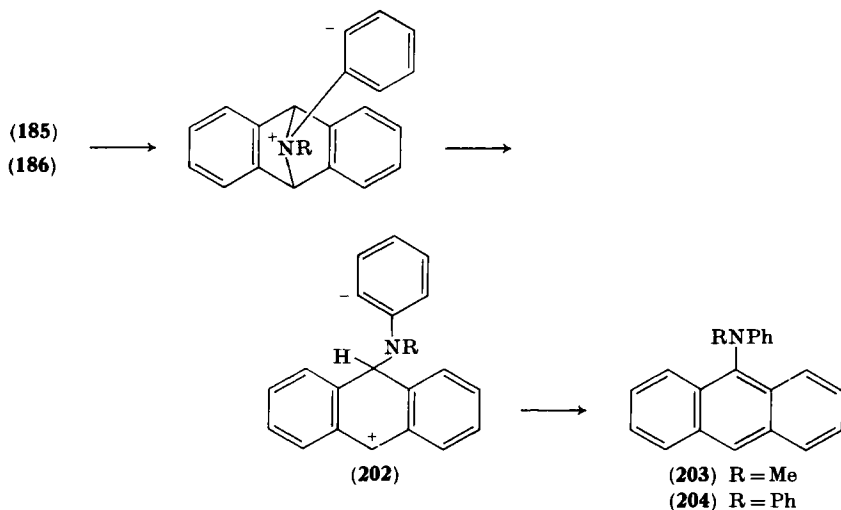
Compounds **185** and **190** add methyl iodide to give crystalline quaternary salts,^{101, 102} one of which (**196**) resolidifies on heating above its melting point 130°, possibly forming the isomeric salt **198**.

The quaternary hydroxide (**197**) obtained from **196** with moist silver oxide rearranges to a mixture (~ 1:9) of *cis*- and *trans*-9-dimethylamino-10-hydroxy-9,10-dihydroanthracene (**200**).¹⁰¹ *Cis* stereochemistry was assigned to the higher melting isomer on account of the intramolecular hydrogen bonding evident from the IR spectrum, which requires that both substituents be in the "flagpole" positions as in partial structure **201**. Decomposition of **197** in water at 20° is kinetically first order, and the rate is independent of the hydroxide ion concentration.¹⁰¹ A rate-determining step involving ring-opening to the cation **199** is indicated.

Benzynes reacts with **185** to give 17% of the ring-opened 1:1 adduct (**203**) and 9% of anthracene.¹⁰¹ The formation of **203** is explained by a



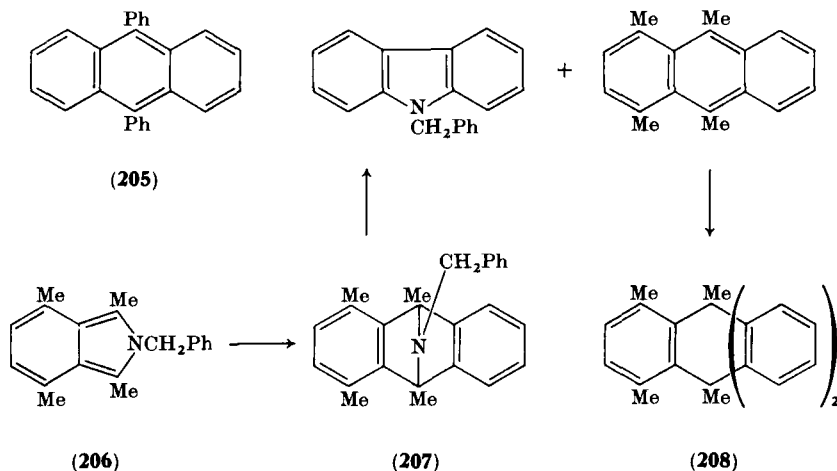
mechanism involving electrophilic attack of benzyne at the nitrogen atom of **185** and ring-opening to the zwitterion **202**, as for **197** \rightarrow **199**. In this case, however, intermediate **202** is quenched by an intramolecular



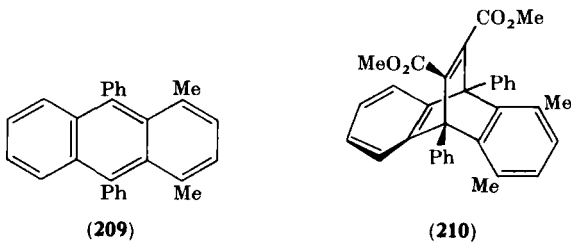
shift of a proton from the 9-position. The formation of 17% of 9-diphenyl-aminoanthracene (**204**) alongside the 1:1 adduct (**186**) from *N*-phenyl-indole and benzyne is attributable to phenylation of **186** by reaction with benzyne in the same way.¹⁰¹

D. DEAMINATION REACTIONS

Both compounds **190** and **193** are reduced to 9,10-diphenylanthracene (**205**) by zinc and acetic acid.^{101, 102} However, more interest attaches to the formation of anthracenes from anthracen-9,10-imines in nonreducing conditions. The *N*-ethoxycarbonyl derivative (**192**) decomposed at 215° in cyclohexane to 33% of **205**,⁶³ although curiously this product was not obtained if the solvent was previously degassed. Whether or not the reaction involves simple extrusion of ethoxycarbonyl nitrene could not be established, since the expected *N*-cyclohexylurethane was not detected.⁶³ The 9,10-epithioanthracene (**194**) loses sulfur thermally to give **205**.¹⁰¹



The formation of anthracene in reactions of **185** and **186** with benzyne, which was unexplained by Wittig *et al.*,¹⁰¹ possibly is due to an alternative reaction of the intermediate zwitterion (**202**) with another molecule of benzyne or with a benzyne precursor. Benzyne reacted with the isoindole (**206**) to give the tetramethyltritycene (**208**) and, in a separate run using excess of the benzyne precursor, *N*-benzylcarbazole.⁹⁹ The latter product would appear to be made up of the *N*-benzyl group from an intermediate anthracen-9,10-imine (**207**) and two molecules of benzyne. Mass spectral evidence also implicated the adduct **207**, and the formation of **208** was attributed to benzyne-induced deamination of **207** to 1,4,9,10-tetramethylantracene, which was trapped by further addition of benzyne across the 9- and 10-positions.



In a related reaction (see also Section III, H) the anthracen-9,10-imine (**187**) with dimethyl acetylenedicarboxylate at 180° gave 26% 1,4-dimethyl-9,10-diphenylanthracene (**209**) and 14% of its Diels-Alder adduct with the acetylenic ester, the 9,10-ethenoanthracene (**210**).⁹⁹ No nitrogen-containing product was isolated, and the related compounds **188** and **189** failed to react with the acetylenic ester.

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Advances in Homolytic Substitution of Heteroaromatic Compounds

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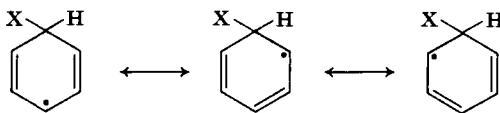
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I. Introduction

Homolytic aromatic substitution was long considered a relatively unimportant branch of aromatic substitution although it was the subject of numerous studies and is undoubtedly of theoretical interest for an understanding of aromatic reactivity. This lack of interest was mainly

due to the fact that (1) the radical sources were not always easily available, (2) the yields were poor, and, above all, (3) to the isomer selectivity of the reactions were poor. This low selectivity led to complex mixtures of isomers and it was possible to avoid the formation of polysubstituted products only with very low conversion ratios.

This rather discouraging picture arose mainly because of an over-concentration on homolytic aromatic arylation, the results of which had a distorting influence on the development of homolytic aromatic substitution reactions generally. It was recently realized that polar factors play a more important role in some homolytic aromatic substitutions than foreseeable on the basis of a transition state similar to the σ -complex



and the possibility of reactions of much greater synthetic potential was then apparent.

Two reaction methods proved very fruitful: the use of radicals with a strong polar character and the use of aromatic substrates of strongly electron-deficient character such as compounds with a positive charge in the aromatic ring. Particularly interesting results were obtained with amino radical cations, which can easily be obtained from *N*-chloroamines, and with protonated heteroaromatic bases which showed a high selectivity with nucleophilic radicals. While homolytic aromatic substitution is of great interest in the homocyclic aromatic series,¹ with a selectivity and versatility comparable to that of electrophilic substitution, the utility is rather lower in the heteroaromatic series owing to the very strongly electrophilic character of the radical species and the necessity to work in a very strongly acidic medium to produce the amino radical cations. Correspondingly, homolytic substitutions with nucleophilic radicals are of great importance for protonated heteroaromatic bases but of lesser interest using nonprotonated heteroaromatic bases and homocyclic aromatic substrates. Among these nucleophilic radicals the use of alkyl, acyl, carbamoyl, α -oxyalkyl, and α -*N*-alkyl radicals have proved to be very successful. The aryl radicals were widely used in obtaining a deeper understanding of the homolytic arylation of heteroaromatics, but the sensitivity to polar effects is too low to give significant selectivity from the synthetic point of view.

¹ F. Minisci, *Chim. Ind. (Milan)* **49**, 705 (1967). *Synthesis*, 1 (1973); G. Sosnovsky and D. J. Rawlinson. *Advan. Free Radical Chem.* **4**, 203 (1972).

Thus the overall picture of homolytic substitution of heteroaromatic compounds has undergone only minor modification as regards arylation, but very great modification as regards substitution with nucleophilic radicals, since Norman and Radda² reviewed the field in these Advances.

II. Alkylation

A. INTRODUCTION

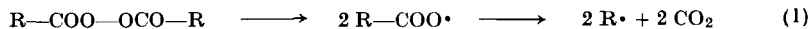
Homolytic alkylation of homocyclic aromatic substrates is of much less interest than homolytic arylation because, in addition to the low selectivity, which also characterizes arylation, yields are usually poor, due to side reactions which compete seriously with the simple substitution reaction. The behavior of nonprotonated heteroaromatic substrates is similar. The case is quite different with protonated heteroaromatic bases because side reactions are eliminated or minimized, yields are generally good, and, above all, the selectivity is very high.³ Moreover, very versatile and easily available sources of alkyl radicals can be used under simple experimental condition; it follows that homolytic alkylation of protonated heteroaromatic bases can be considered one of the main reactions of this class of compounds.

B. SOURCES OF ALKYL RADICALS

1. Peroxides

A wide variety of peroxides have been used to produce alkyl radicals, either directly as fragments of the decomposition of peroxides, or indirectly by hydrogen abstraction from suitable solvents. The production of alkyl radicals used in homolytic alkylation has been accomplished by thermal or photochemical homolysis and recently also by redox reactions due to the possibilities offered by alkylation in acidic aqueous solution.

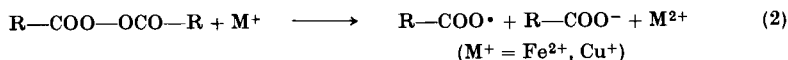
a. *Acyl Peroxides.* The acyl peroxides are a very clean source of alkyl radicals; the thermal homolysis takes place according to Eq. (1). A



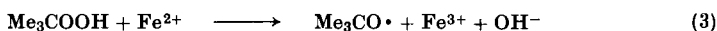
² R. O. C. Norman and G. K. Radda, *Advan. Heterocycl. Chem.* **2**, 131 (1963).

³ F. Minisci, R. Galli, M. Cecere, V. Malatesta, and T. Caronna, *Tetrahedron Lett.* 5609 (1968).

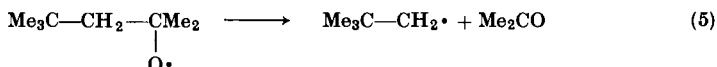
disadvantage of this source is the fact that usually more than 50% of the radicals react within the solvent cage and are not available for the homolytic alkylation reaction. However, in the presence of protonated heteroaromatic bases an induced free-radical chain produces high yields of alkylation products and only traces of products of "cage combination."⁴ Acyl peroxides have also been used for alkylation of heteroaromatic bases by redox decomposition^{4, 5} [Eq. (2)].



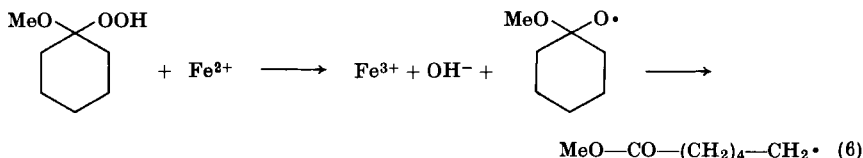
b. *Alkyl Hydroperoxides.* Alkyl hydroperoxides and ferrous salts have been used for the alkylation of heteroaromatic bases in aqueous solutions, e.g., *t*-butyl hydroperoxide as a source of methyl radical^{6, 7} [Eqs. (3) and (4)], and 2,4,4-trimethyl-2-hydroperoxypentane,⁶ ob-



tained by addition of hydrogen peroxide to diisobutylene, as a source of neopentyl radical [Eq. (5)].



c. *1-Oxyhydroperoxides.* Peroxides of the oxyhydro type are obtained by the addition of hydrogen peroxide to ketones. High yields of alkyl radicals are then often obtained by reaction with ferrous salts. 1-Methoxycyclohexyl hydroperoxide is easily obtained from cyclohexanone and hydrogen peroxide in methanol. It gives rise to the 5-(methoxycarbonyl)-pentyl radical, which has been used to alkylate protonated heteroaromatic bases in high yield^{3, 6} [Eq. (6)].



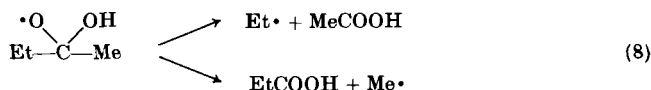
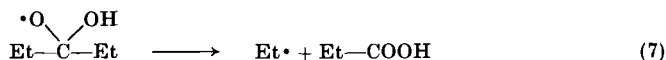
⁴ F. Minisci, A. Selva, O. Porta, P. Barilli, and G. P. Gardini, *Tetrahedron* **28**, 2415 (1972).

⁵ G. P. Gardini and F. Minisci, *Ann. Chimica (Rome)* **60**, 746 (1970).

⁶ F. Minisci, R. Galli, V. Malatesta, and T. Caronna, *Tetrahedron* **26**, 4083 (1970).

⁷ G. P. Gardini, F. Minisci, and G. Palla, *Chim. Ind. (Milan)* **53**, 263 (1971).

Acyclic ketones have also been used: diethyl ketone as a source of ethyl radicals⁶ [Eq. (7)], and methyl ethyl ketone as a source of mainly ethyl radicals, and, to a minor extent, of methyl radicals⁷ [Eq. (8)].



d. *Alkyl Peroxides*. The thermal homolysis of *t*-butyl peroxide has been used as source of methyl radicals⁸⁻¹⁰ [Eq. (9)].



e. *Hydrogen Abstraction from Solvents*. Peroxides have been used to produce alkyl radicals by hydrogen abstraction from solvents¹¹⁻¹³ (cycloalkanes, toluene, heptane). *t*-Butyl peroxide, and benzoyl peroxide and percarbonate have all been successfully utilized. The usefulness of the method is obviously limited by the selectivity of the abstracting species. Thus *n*-heptane is of very little interest because four different radicals are generated.

2. Carboxylic Acids

The oxidative decarboxylation of carboxylic acids is the most convenient source for the alkylation of protonated heteroaromatic bases owing to their easy availability and the high versatility of the reaction, which permits methyl, primary, secondary, and tertiary alkyl radicals to be obtained under very simple experimental conditions. The following methods have been utilized.

a. *Silver-Catalyzed Decarboxylation by Peroxydisulfate*. This is the simplest method; it allows the reaction to be carried out in aqueous

⁸ K. Schwetlich and R. Lungwitz, *Chem. Ztg.* **4**, 458 (1964).

⁹ K. C. Bass and P. Nababsing, *J. Chem. Soc. C*, 2169 (1970).

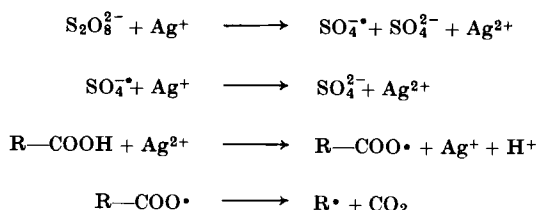
¹⁰ H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1021 (1971).

¹¹ G. Vernin, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci. Ser. C* **272**, 854 (1971).

¹² H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. Chim. Fr.*, 3553 (1971).

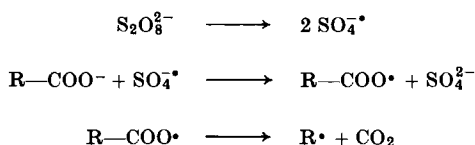
¹³ J. Hutton and W. A. Waters, *J. Chem. Soc.*, 4253 (1965).

acidic solution¹⁴⁻¹⁷ Alkyl radicals are formed according to the mechanism of Scheme 1.



SCHEME 1

b. *Decarboxylation of Carboxylate Ions by Peroxydisulfate.* In acidic medium decarboxylation of carboxylic acids by peroxydisulfate generally does not occur in the absence of silver salts. However, by using an aqueous solution of carboxylic acid and sodium carboxylate, decarboxylation can occur in the absence of a silver salt according to the mechanism of Scheme 2.



SCHEME 2

This method can be used with heteroaromatic bases, such as thiazoles or pyrazines, which complex with the silver salt and reduce its catalytic activity.¹⁸ A disadvantage of the method is that the heteroaromatic base can be only partially protonated under these conditions.

c. *Decarboxylation of Lead Carboxylates.* This method^{5, 9, 18-20} involves either the preparation and thermal decomposition of the lead

¹⁴ F. Minisci, R. Bernardi, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron* **27**, 3575 (1971).

¹⁵ F. Bertini, R. Galli, F. Minisci, and O. Porta, *Chim. Ind. (Milan)* **54**, 223 (1972).

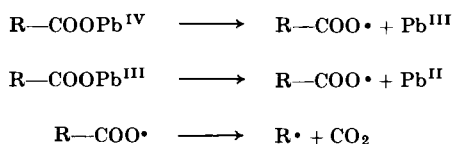
¹⁶ F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *Tetrahedron* **28**, 2403 (1972).

¹⁷ T. Caronna, G. Fronza, F. Minisci, O. Porta, and G. P. Gardini, *J. Chem. Soc., Perkin Trans. II* 1477 (1972).

¹⁸ F. Bertini, T. Caronna, R. Galli, F. Minisci, and O. Porta, *Chim. Ind. (Milan)* **54**, 425 (1972).

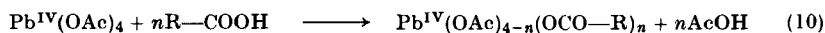
¹⁹ R. A. Abramovitch and K. Kenaschuk, *Can. J. Chem.* **45**, 509 (1967).

²⁰ K. C. Bass and P. Nababsing, *J. Chem. Soc. C*, 388 (1969).



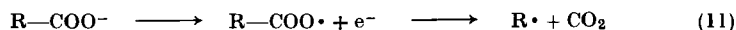
SCHEME 3

salts (Scheme 3), or the oxidation of carboxylic acids by lead tetraacetate in which case decarboxylation follows a preequilibration [Eq. (10)].



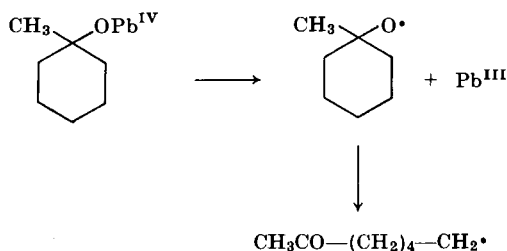
The formation of lead salts *in situ* from Pb_3O_4 and carboxylic acids is a further variant which avoids the rather tedious operations of preparation and isolation of the salts.

d. *Electrolytic Decarboxylation*. Electrolysis of salts of carboxylic acids gives free radicals according to Eq. (11).



3. Alcohols

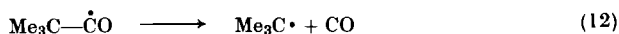
Oxidation of tertiary alcohols by lead tetraacetate gives alkyl radicals by β -scission of the initially formed alkoxy radicals. The reaction has been used to alkylate protonated heteroaromatic bases using 1-methylcyclohexanol.¹⁸ (Scheme 4).



SCHEME 4

4. Aldehydes

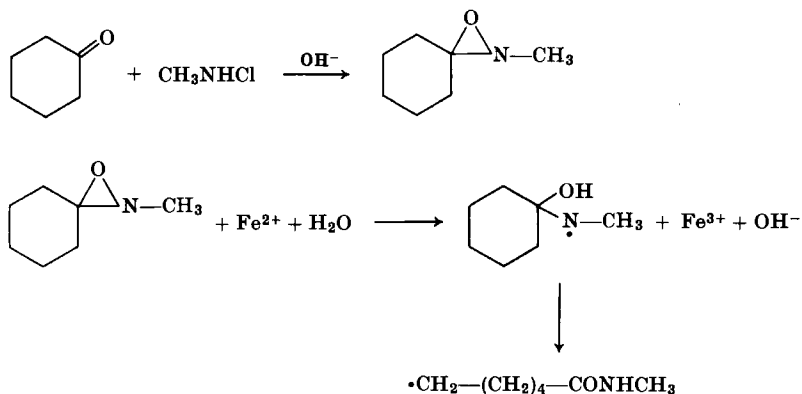
The acyl radicals obtained by hydrogen abstraction from aldehydes easily attack protonated heteroaromatic bases. With secondary and tertiary acyl radicals decarbonylation competes with the aromatic acylation²¹ [Eq. (12)].



²¹ T. Caronna, R. Galli, V. Malatesta, and F. Minisci, *J. Chem. Soc. C*, 1747 (1971).

5. Oxaziranes

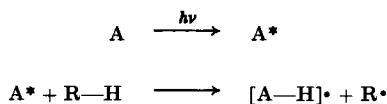
Some oxaziranes can be prepared very simply from ketones and *N*-chloroamines. Thus 2-methyl-3,3-pentamethyleneoxazirane is easily obtained from cyclohexanone and *N*-methylchloramine; its reduction by ferrous salts gives an alkyl radical, which has been used to alkylate, in high yield, protonated heteroaromatic bases in aqueous solution^{3, 6} (Scheme 5).



SCHEME 5

6. Photochemical and γ -Ray-Induced Processes

Recently numerous homolytic alkylations of heteroaromatics have been carried out by photochemical and γ -ray-induced processes. The photochemical process involves hydrogen abstraction from various hydrogen donors (RH) by the excited state of the heteroaromatic (A) (Scheme 6).



SCHEME 6

7. Organometallic Compounds

Thermal and photochemical decomposition of organomercury and organolead compounds has been used to produce alkyl radicals for the homolytic alkylation of heteroaromatics. Dibenzylmercury has been

particularly studied because it is easily available and is decomposed under simple conditions.²⁰

C. PRODUCTS OF ALKYLATION

All the radical sources described above have been used in the homolytic alkylation of heteroaromatic compounds. The data concerning alkylation are summarized in Tables I and II; only the reports referring to better yields of products are included, except for the cases where a compound has been alkylated by more than one method. These results show the great importance of the acidity of the reaction medium. With nonprotonated heteroaromatics the reaction is of little interest because conversions, yields, and selectivity are always low. With protonated heteroaromatic bases the homolytic alkylation is of great synthetic interest, comparable with that of electrophilic alkylation in the homocyclic series. Alkylation in acidic aqueous solution has proved to be particularly convenient by using easily available peroxides and oxaziranes^{3, 6} and above all by utilizing the oxidative decarboxylation of carboxylic acids by peroxydisulfate.¹⁴ Synthetic interest arises from the fact that this latter source of alkyl radicals is cheap, readily available, and very versatile. Yields are good and the experimental conditions are particularly simple; the reaction is carried out in aqueous solution at moderate temperatures. The selectivity of the attack is complete in positions α and γ to the protonated heterocyclic nitrogen and when only one of these positions is free, nearly quantitative conversions of the heterocyclic substrates can be obtained without appreciable formation of polysubstitution products. This high selectivity is due to the nucleophilic character of the alkyl radicals, which also allows the introduction, in high yield, of *t*-alkyl groups which could not be introduced by homolytic substitution in homocyclic systems.²² Moreover, substitution occurs without rearrangement, even in the case of neopentyl radical, and without isomerization, which frequently takes place in electrophilic alkylation. This last reaction, which is very important in the homocyclic series, is not applicable with heteroaromatic bases, and in any case would cause a completely different orientation. Also, nucleophilic alkylation with organometallic reagents (Grignard reagents, lithium alkyl) gives good results in only a few cases. Homolytic alkylation in acidic medium must therefore be considered as an important reaction of heteroaromatic bases.

²² J. R. Shelton and C. W. Uzelmeyer, *J. Amer. Chem. Soc.* **88**, 5222 (1966).

TABLE I
HOMOLYTIC ALKYLATION OF HETEROCYCLIC COMPOUNDS IN NONACIDIC MEDIUM^a

Heterocyclic compound	Alkyl radical	Radical source	Method (Section II, B)	Position of substitution (%)	Yield (%)	Ref.
Pyridine	Methyl	Acetyl peroxide	1, a	2(63); 3(20)	30 ^b	19
	Methyl	Pb(OAc) ₄	2, c	2(62); 3(21); 4(17)	10.7 ^b	19
	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	2(58); 3(23); 4(19)	13.5 ^b	8
	Cyclohexyl	Cyclohexane	1, e	2(65); 3 + 4(35)	—	11
	Benzyl	Pb(OCOCH ₂ Ph) ₄	2, c	2(83); 4(17)	0.6 ^b	20
3-Methylpyridine	Methyl	Acetyl peroxide	1, a	2(56); 4(20); 5(5); 6(19)	23.8 ^b	19
4-Methylpyridine	Methyl	Acetyl peroxide	1, a	2(64); 3(36)	12.5 ^b	19
	Methyl	<i>t</i> -BuO ₂	1, d	2(65); 3(35)	—	8
	Cyclohexyl	Cyclohexane	1, e	2(73); 3(27)	—	11
	Cyclohexyl	Cyclohexane	1, e	2(93); 3(7)	—	12
2,6-Dimethylpyridine	Cyclohexyl	Cyclohexane	1, e	3(84); 4(16)	—	11
3,5-Dimethylpyridine	Cyclohexyl	Cyclohexane	1, e	2(60); 4(40)	—	11
Quinoline	Methyl	<i>t</i> -BuO ₂	1, d	2(10); 4(24); 5(16); 8(31); 3 + 6 + 7(19)	34.7 ^b	9
	Methyl	Pb(OAc) ₄	2, c	2(9); 4(23); 5(18); 8(32); 3 + 6 + 7(18)	19 ^b	9

Isoquinoline	Benzyl	(PhCH ₂) ₂ Hg	7	2(33); 4(45); 2,4(22)	1.8	20
	Benzyl	(PhCH ₂ COO) ₄ Pb	2,c	2(56); 4(42); 2,4(2)	4.3 ^b	20
	Benzyl	(PhCH ₂ COO) ₄ Pb	2,c	1(98); 3 + 4(2)	6.5 ^b	20
	Benzyl	(PhCH ₂) ₂ Hg	7	1(54); 3(31); 4(15)	1.3 ^b	20
	Methyl	<i>t</i> -BuO ₂	1,d	1	4.5 ^b	9
Indole	Methyl	Pb(OAc) ₄	2,c	1	6.7 ^b	9
	Benzyl	Toluene	1,e	1(26); 3(33); 4(12); 1,3(12); 2,3(17)	5.8 ^b	13
Thiazole	Cyclohexyl	Cyclohexane	1,e	2(73); 4(14); 5(13)	—	11
2-Methylthiazole	Cyclohexyl	Cyclohexane	1,e	4(44); 5(56)	—	11
4-Methylthiazole	Cyclohexyl	Cyclohexane	1,e	2(84); 5(16)	—	11
	Cyclohexyl	Cyclohexane	1,e	2(95); 5(5)	Low	23
5-Methylthiazole	Cyclohexyl	Cyclohexane	1,e	2(90); 4(10)	—	11
2,4-Dimethylthiazole	Cyclohexyl	Cyclohexane	1,e	5	—	11
2,5-Dimethylthiazole	Cyclohexyl	Cyclohexane	1,e	4	—	11
4,5-Dimethylthiazole	Cyclohexyl	Cyclohexane	1,e	2	Low	11, 13

^a Conversion in all of these reactions was very low, < 5%.

^b Based on the radical source.

TABLE II
HOMOLYTIC ALKYLATION OF HETEROCYCLIC COMPOUNDS IN ACIDIC MEDIUM

Heterocyclic compound	Alkyl radical	Radical source	Method (Section II, B)	Position of substitution (%)	Conversion (%)	Yield (%)	Ref.
Pyridine	Methyl	<i>t</i> -BuOOH	1, b	2(30); 4(70)	13	~ Quantitative ^b	6
	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	2(78); 4(22)	—	—	10
	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	2(93); 4(7)	Very low	11.8 ^a	9
	Methyl	Pb(OAc) ₄	2, c	2(76); 3(3); 4(21)	Very low	12.9 ^a	9
	Methyl	CH ₃ COOH	2, a	2 and 4	Very low	~ Quantitative ^b	16
	Ethyl	CH ₃ CH ₂ COOH	2, a	2; 4; 2,4; 2,6; 2,4,6	100	98 ^b	14
	Ethyl	EtCOEt	1, c	2(25); 4(75)	20	~ Quantitative ^b	6
	Propyl	CH ₃ (CH ₂) ₂ COOH	2, a	2 and 4	Very low	~ Quantitative ^b	16
	Butyl	CH ₃ (CH ₂) ₃ COOH	2, a	2 and 4	Very low	~ Quantitative ^b	16
	Isobutyl	EtCH(Me)COOH	2, a	2 and 4	Very low	~ Quantitative ^b	16
	Cyclohexyl	C ₆ H ₁₁ COOH	2, a	2(37); 4(63)	14	~ Quantitative ^b	14
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2(32); 4(68)	18	~ Quantitative ^b	14
	Benzyl	(PhCH ₂) ₂ Hg	7	2(76); 4(24)	Very low	35 ^a	20
	5-(Methyl-amino-carbonyl)-pentyl	2-Methyl-3,3-pentamethylene oxazirane	5	2; 4 and a dimer	20	~ Quantitative ^b	3, 6
	5-(Methoxy-carbonyl)-pentyl	1-Methoxycyclohexyl hydroperoxide	1, c	2(34); 4(66)	—	—	6
4-Cyano-pyridine	Methyl	CH ₃ COOH	2, a	2(85); 2,6(15)	42	82 ^b	14
	Methyl	<i>t</i> -BuOOH	1, b	2	Very low	~ Quantitative ^b	7
	Benzyl	PhCH ₂ COOH	2, a	2; 2,6	85	94 ^b	42

	Ethyl	CH ₃ CH ₂ COOH	2, a	2(78); 2,6(22)	77	81 ^b	14
	Propyl	CH ₃ (CH ₂) ₂ COOH	2, a	2	Very low	~ Quantitative ^b	16
	Isopropyl	Me ₂ CHCOOH	2, a	2(67); 2,6(33)	86	88 ^b	14
	Butyl	BuCOOH	2, a	2	Very low	~ Quantitative ^b	16
	Isobutyl	EtCH(Me)COOH	2, a	2	Very low	~ Quantitative ^b	16
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2(87); 2,6(13)	95	98 ^b	14
2-Methyl- pyridine	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	6(74); 4(24); 4,6(2)	—	—	10
4-Methyl- pyridine	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	2(98); 2,6(2)	—	—	10
	Methyl	<i>t</i> -BuOOH	1, b	2	Very low	~ Quantitative ^b	7
	Methyl	MeCOOH	2, a	2	Very low	~ Quantitative ^b	16
	Propyl	PrCOOH	2, a	2	Very low	~ Quantitative ^b	16
	Butyl	BuCOOH	2, a	2	Very low	~ Quantitative ^b	16
	Isobutyl	EtCH(Me)COOH	2, a	2	Very low	~ Quantitative ^b	16
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2	Very low	~ Quantitative ^b	16
4-Methoxy- pyridine	Methyl	MeCOOH	2, a	2	Very low	~ Quantitative ^b	16
	Methyl	<i>t</i> -BuOOH	1, b	2	Very low	~ Quantitative ^b	7

(continued)

TABLE II—*continued*

Heterocyclic compound	Alkyl radical	Radical source	Method (Section II, B)		Position of substitution (%)	Conversion (%)	Yield (%)	Ref.
4-Chloro-pyridine	Propyl	PrCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Butyl	BuCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Isobutyl	EtCH(Me)COOH	2, a	2		Very low	~ Quantitative ^b	16
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Methyl	MeCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Methyl	<i>t</i> -BuOOH	1, b	2		Very low	~ Quantitative ^b	7
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2		Very low	~ Quantitative ^b	16
4-Acetyl-pyridine	Benzyl	PhCH ₂ COOH	2, a	2; 2,6		80	87 ^b	42
	Methyl	MeCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Methyl	<i>t</i> -BuOOH	1, b	2		Very low	~ Quantitative ^b	7
	Propyl	PrCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Butyl	BuCOOH	2, a	2		Very low	~ Quantitative ^b	16
	Isobutyl	EtCH(Me)COOH	2, a	2		Very low	~ Quantitative ^b	16
	<i>t</i> -Butyl	BuCOOH	2, a	2		Very low	~ Quantitative ^b	16

Quinoline	Methyl	MeCOOH	2, a	2(23); 4(25); 2,4(52)	97	~ Quantitative ^b	14
	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	2(49); 4(50)	Very low	34.2 ^a	9
	Methyl	<i>t</i> -BuOOH	1, b	2(42); 4(38); 2,4(20)	76	~ Quantitative ^b	6
	Ethyl	EtCOOH	2, a	2(21); 4(25); 2,4(54)	97	~ Quantitative ^b	14
	Propyl	PrCOOH	2, a	2(28); 4(36); 2,4(36)	87	~ Quantitative ^b	14
	Butyl	BuCOOH	2, a	2(27); 4(36); 2,4(37)	99	~ Quantitative ^b	14
	Ethyl	EtCOEt	1, c	2(58); 4(42)	17	~ Quantitative ^b	6
	Isopropyl	Me ₂ CHCOOH	2, a	2(13); 4(26); 2,4(61)	99	~ Quantitative ^b	14
	Isopropyl	Me ₂ CHCOOH	2, c	2(38); 4(42); 2,4(20)	57	~ Quantitative ^b	18
	Isopropyl	Me ₂ CHC(Me) ₂ OH	3	2 and 4	—	—	18
	Cyclohexyl	C ₆ H ₁₁ COOH	2, a	2(24); 4(35); 2,4(41)	100	~ Quantitative ^b	14
	Isobutyl	Isovaleroyl- peroxide	1, a	2(25); 4(33); 2,4(42)	70	~ Quantitative ^b	4
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2	98	95 ^b	14
	Nonyl	Decanoyl peroxide	1, a	2 and 4	Low	97 ^a	4
	Benzyl	(PhCH ₂) ₂ Hg	7	2(50); 4(45); 2,4(5)	Low	34.7 ^a	20
	5-(Methyl- amino- carbonyl- pentyl)	2-Methyl-3,3- pentamethylene oxazirane	5	2(53); 4(47)	40	~ Quantitative ^b	3
	5-(Methoxy- carbonyl- pentyl)	1-Methoxycyclo- hexyl hydro- peroxide	1, c	2(54); 4(46)	12	~ Quantitative ^b	3, 6
	5-Keto- heptyl	1-Methylcyclo- hexanol	3	2 and 4	—	—	18
2-Methyl quinoline	Methyl	MeCOOH	2, a	4	72	90 ^b	14
	Ethyl	EtCOOH	2, a	4	98	~ Quantitative ^b	14
	Propyl	PrCOOH	2, a	4	98	90 ^b	14

(continued)

TABLE II—*continued*

Heterocyclic compound	Alkyl radical	Radical source	Method (Section II, B)		Position of substitution (%)	Conversion (%)	Yield (%)	Ref.
4-Methyl-quinoline	Isopropyl	Me ₂ CHOOH	2, a	4		100	93 ^b	14
	Isopropyl	Me ₂ CHOH	2, b	4		98	70 ^b	18
	Butyl	BuCOOH	2, a	4		Low	~ Quantitative ^b	17
	Isobutyl	EtCH(Me)COOH	2, a	4		Low	~ Quantitative ^b	17
	Cyclopropyl	C ₃ H ₅ COOH	2, a	4		30	~ Quantitative ^b	14
	Isobutyl	EtCH(Me)COOH	2, a	2		Low	~ Quantitative ^b	17
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2		Low	~ Quantitative ^b	17
Isoquinoline	Methyl	<i>t</i> -Bu ₂ O ₂	1, d	1		Very low	11.7 ^a	9
	Methyl	Pb(OAc) ₄	2, c	1		Very low	19.3 ^a	9
	Ethyl	EtCOOH	2, a	1		33	~ Quantitative ^b	14
	Cyclohexyl	C ₆ H ₁₁ COOH	2, a	1		99	84 ^b	14
	Benzyl	(PhCH ₂) ₂ Hg	7	1(98); 3 + 4(1)		Very low	49.6 ^a	20
	5-(Methyl-amino-carbonyl) pentyl	2-Methyl-3,3-pentamethylene oxazirane	5	1		—	—	3
Acridine	Methyl	MeCOOH	2, a	9		11	~ Quantitative ^b	14
	Ethyl	EtCOOH	2, a	9		24	~ Quantitative ^b	14
	Butyl	BuCOOH	2, a	9		37	~ Quantitative ^b	14
	Isopropyl	Me ₂ CHCOOH	2, a	9		66	~ Quantitative ^b	14

	5-(Methyl-amino-carbonyl) pentyl	2-Methyl-3,3-pentamethylene oxazirane	5	9	—	—	3
	5-(Methoxy-carbonyl) pentyl	1-Methoxycyclohexyl hydroperoxide	1, c	9	—	—	3
Quinoxaline	Propyl	PrCOOH	2, b	2(76); 2,3(24)	82	66 ^b	18
	Isopropyl	Me ₂ CHCOOH	2, b	2(88); 2,3(12)	86	68	18
	Isopropyl	Me ₂ CHCOOH	2, b	2(81); 2,3(19)	63	~ Quantitative ^b	18
	Butyl	BuCOOH	1, a; 2, c	2	—	—	5
	Isobutyl	EtCH(Me)COOH	1, a; 2, c	2	—	—	5
	<i>t</i> -Butyl	Me ₃ CCOOH	2, c	2	90	78 ^b	18
	Benzyl	(PhCH ₂) ₂ Hg	7	2	Very low	54 ^a	24
	Benzyl	PhCH ₂ COOH	2, a; 2, c	2	60–90	65–92 ^b	42
Pyrazine	5-(Methyl-amino-carbonyl) pentyl	2-Methyl-3,3-pentamethylene oxazirane	5	2	—	—	3
2-Amino-pyrimidine	5-(Methyl-amino-carbonyl) pentyl	2-Methyl-3,3-pentamethylene oxazirane	5	4	—	—	3
Thiazole	Methyl	Pb(OAc) ₄	2, c	2(86); 5(14)	—	—	25
4-Methyl-thiazole	Methyl	Pb(OAc) ₄	2, c	2(77); 5(17); 2,5(6)	—	22 ^c	25
5-Methyl-thiazole	Methyl	Pb(OAc) ₄	2, c	2	—	15 ^c	25
Benzothiazole	Propyl	PrCOOH	2, b	2	80	65 ^b	18
	Isopropyl	Me ₂ CHCOOH	2, b	2	80	67 ^b	18

[Sec. II.C.]

HOMOLYTIC AROMATIC SUBSTITUTION

(continued)

TABLE II—*continued*

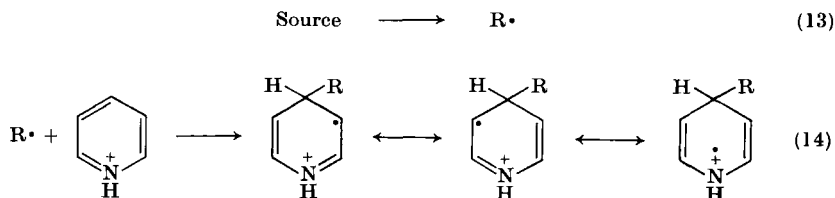
Heterocyclic compound	Alkyl radical	Radical source	Method (Section II, B)		Position of substitution (%)	Conversion (%)	Yield (%)	Ref.
Imidazole	Isopropyl	Me ₂ CHCOOH	2, c	2		34	71 ^b	18
	<i>t</i> -Butyl	Me ₃ CCOOH	2, b	2		70	74 ^b	18
	<i>t</i> -Butyl	Me ₃ CCHO	4	2		80	48 ^b	21
	Isopropyl	Me ₂ CHCOOH	2, a	2		—	88 ^c	15
	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2		—	80 ^c	15
Benzimidazole	Propyl	PrCOOH	2, a	2		—	50 ^c	15
	Isopropyl	Me ₂ CHCOOH	2, a	2		—	54 ^c	15
	Cyclohexyl	C ₆ H ₁₁ COOH	2, a	2		—	70 ^c	15
5-Chlorobenzimidazole	<i>t</i> -Butyl	Me ₃ CCOOH	2, a	2		—	68 ^c	15
	Isopropyl	Me ₂ CHCOOH	2, a	2		—	78 ^c	15

^a Based on the radical source.^b Based on the converted heterocyclic compound.^c Based on the used heterocyclic compound; conversions are not generally quantitative.²³ M. Baule, G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 2083 (1971).²⁴ K. C. Bass and P. Nababsing, *Org. Prep. Proc. Int.* **3**, 45 (1971).²⁵ H. J. M. Dou, *Bull. Soc. Chim. Fr.*, 1678 (1966).

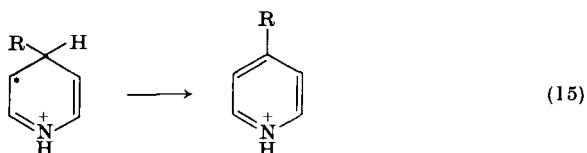
D. MECHANISM OF ALKYLATION

1. *Kinetics and Photochemical Processes*

The mechanism of alkylation is closely connected with the source of the alkyl radicals. The first two steps generally involve the formation of alkyl radicals [Eq. (13)] and their addition to the heteroaromatic ring [Eq. (14)].



The final step of rearomatization of the σ -complex [Eq. (15)] can occur through several paths.



It is influenced by both the nature of the heteroaromatic base and the radical source.

A kinetic study has been carried out in order to elucidate the mechanism by which the σ -complex becomes dehydrogenated to the alkyl heteroaromatic derivative for the alkylation of quinoline by decanoyl peroxide in acetic acid.⁴ The decomposition rates in the presence of increasing amounts of quinoline were determined. At low quinoline concentrations the kinetic course is shown in Fig. 1. The first-order rate constants were calculated from the initial slopes of the graphs and refer to reaction with a quinoline molecule still possessing free 2- and 4-positions. At high quinoline concentration a great increase of reaction rate occurs and both the kinetic course and the composition of the products are simplified. The decomposition rate is first order in peroxide and the nonyl radicals are almost completely trapped by quinoline. The proportion of the nonyl radicals which dimerize to octadecane falls rapidly with increase in quinoline concentration. The decomposition rate in nonprotonated quinoline is much lower than that observed in quinoline in acetic acid.

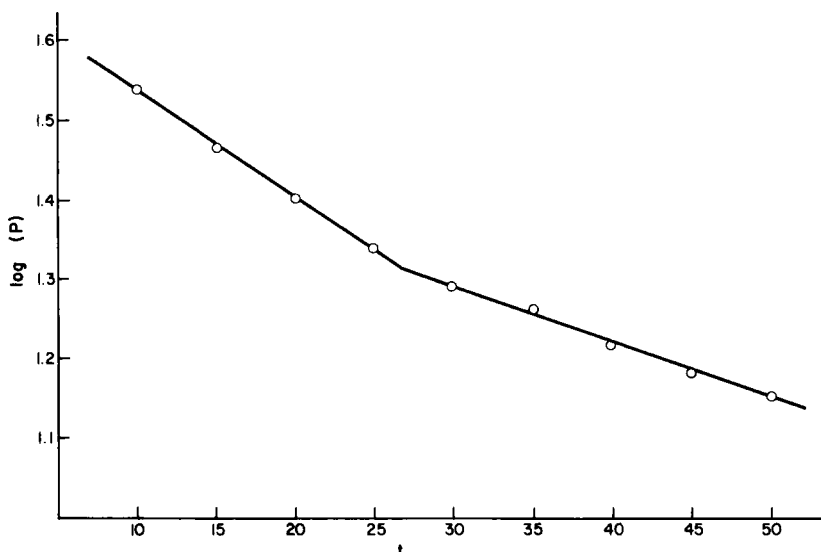
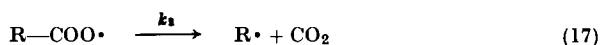
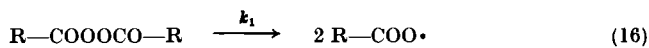


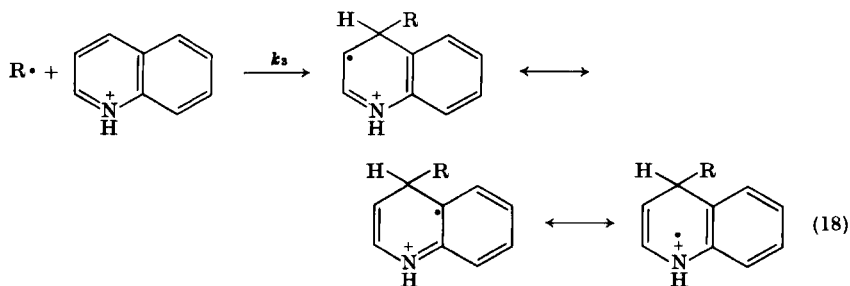
FIG. 1. Kinetics of the decomposition of 0.2 mole of decanoyl peroxide in acetic acid and quinoline at 70°. ⁴

The kinetic course and the formation of the reaction products have been explained by a radical chain mechanism, characterized by the following steps: ⁴

Decomposition of the peroxide [Eqs. (16), (17)]

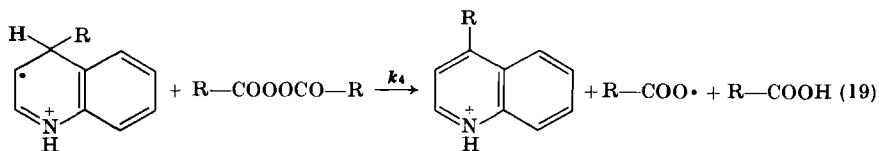


Initiation [(Eq. 18)]

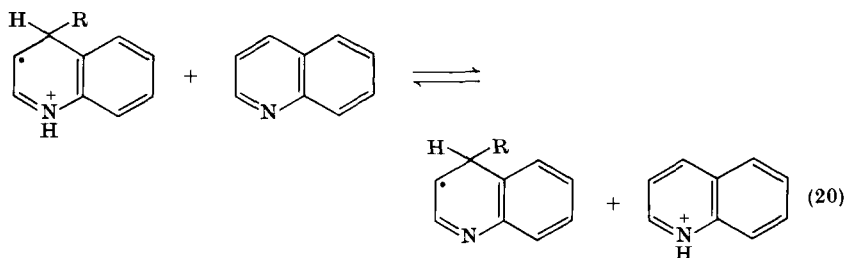


This step is favored by the protonation of the base, owing to the nucleophilic character of the alkyl radical.

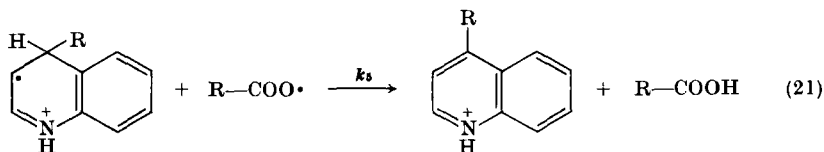
Propagation by induced decomposition of the peroxide [Eq. (19)]



This step is not favored by the protonation of the σ -complex for polar reasons. A fast equilibrium between the protonated σ -complex and the nonprotonated quinoline in acetic acid cannot be excluded, however [Eq. (20)].



A steady-state assumption leads to first-order kinetics in peroxide only if cross-termination takes place according to Eq. (21).



The induced reaction is first order with respect to the peroxide according to the kinetic law of Eq. (22).

$$\frac{-d[\text{P}]}{dt} = k_1[\text{P}] + k_i[\text{P}] \quad (22)$$

A quite different reaction course was observed with benzoyl peroxide. The increase in the decomposition rate on going from nonprotonated to protonated quinoline is relatively small. The high decomposition rate of decanoyl peroxide in the presence of protonated heteroaromatic bases was mainly ascribed to the nucleophilic character of the alkyl radicals, which allows the complete capture of the nonyl radicals escaping from the solvent cage and the consequently rapid induced decomposition. The

much smaller increase in the decomposition rate of benzoyl peroxide in protonated quinoline also agrees with the low selectivity of the phenyl radical with respect to the polar influence of the substrates and the substituents.

With radical sources other than acyl peroxides, the rearomatization of the σ -complex can take place by various, not always well characterized, reactions, such as oxidation by metal salts, hydrogen abstraction by intermediate radicals, disproportionation, and induced decomposition.

Sometimes the reaction medium is not sufficiently oxidizing to allow the complete rearomatization of the σ -complex, which can dimerize. This was observed in the alkylation of pyridine and pyrazine by oxaziridines; the products (**1** and **2**) of the dimerization of the σ -complex and subsequent oxidation were also formed.^{3, 6}



The mechanism of the photochemical alkylation shows particular characteristics as regards the formation of alkyl radicals, the reaction of these radicals with the heteroaromatic substrates, and the rearomatization of the intermediate products. A variety of alkylating agents (hydrocarbons, alcohols, amines, carboxylic acids, amino acids) have been used for photochemical and γ -ray-induced alkylation.²⁶⁻³⁷

There is spectroscopic evidence that the initial step of the photochemical process is hydrogen abstraction by the excited state of the heteroaromatic base [Eq. (23)].

²⁶ E. F. Travededo and V. T. Stenberg, *Chem. Commun.*, 609 (1970).

²⁷ S. Caplain, A. Castellano, J. P. Catteau, and A. Lablache-Combier, *Tetrahedron* **27**, 3541 (1971).

²⁸ A. Castellano and A. Lablache-Combier, *Tetrahedron* **27**, 3541 (1971).

²⁹ F. R. Stermitz, C. C. Wei, and W. H. Huang, *Chem. Commun.*, 482 (1968).

³⁰ F. R. Stermitz, C. C. Wei, and C. M. O'Donnell, *J. Amer. Chem. Soc.* **92**, 2745 (1970).

³¹ A. Stankunas, I. Rosenthal, and J. N. Pitts, *Tetrahedron Lett.*, 4779 (1971).

³² D. Elad and J. Salomon, *Tetrahedron Lett.*, 4783 (1971).

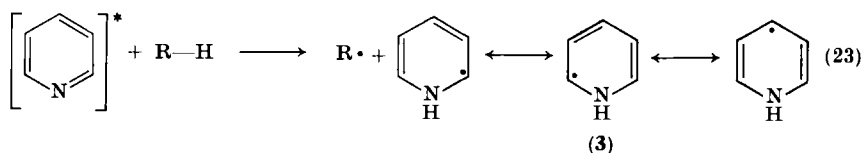
³³ D. Elad and I. Rosenthal, *Chem. Commun.*, 905 (1969).

³⁴ M. Ochiai and K. Morita, *Tetrahedron Lett.*, 2349 (1967).

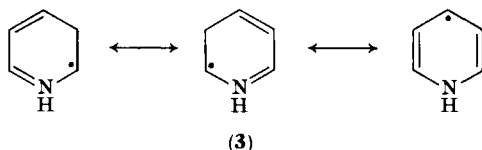
³⁵ H. Nozaki, M. Kato, R. Noyori, and M. Kawaimi, *Tetrahedron Lett.*, 4259 (1967).

³⁶ M. Ochiai, E. Mizuta, Y. Asahi, and K. Morita, *Tetrahedron* **24**, 5861 (1968).

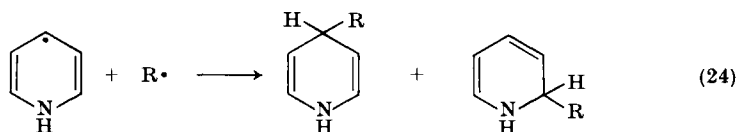
³⁷ T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 3839 (1970).



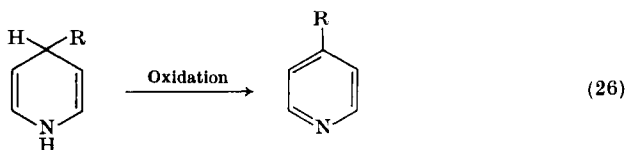
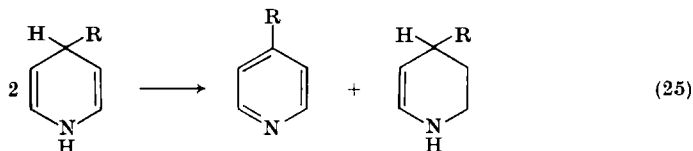
The ESR spectra observed during the reaction have been interpreted on the basis of structure (3).^{27, 38}



Among the mechanisms suggested for the further course of the reaction, simple combination of the radicals thus formed is generally accepted³⁰ [Eq. (24)].



The final products then arise by disproportionation of the dihydro derivatives [Eq. (25)] or by oxidation during the isolation [Eq. (26)].

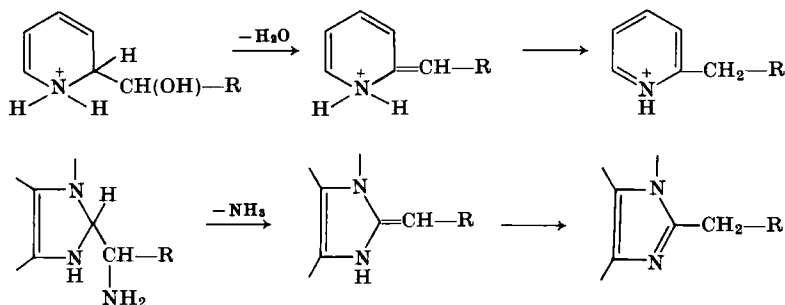


Since alkyl radicals can also attack protonated aromatic bases at the α - and γ -positions, it therefore cannot be excluded that alkylation takes place by both mechanisms: that is, cross-dimerization taking place within the solvent cage and the alkyl radicals escaping from the cage

³⁸ G. Allan, A. Castellano, J. P. Catteau, and A. Lablache-Combier, *Tetrahedron* **27**, 4687 (1971).

reacting with the unexcited protonated base. This could explain some differences observed in acidic and neutral media.³⁰

The alkylation with alcohols and amines can lead to alkyl derivatives or α -hydroxy and α -aminoalkyl derivatives according to the nature of the heteroaromatic base and the reaction conditions. The intermediate products in both cases are, however, the α -hydroxy and α -aminoalkyl dihydro derivatives, which can be aromatized by disproportionation or oxidation, while the loss of water or ammonia leads to the alkyl derivatives (Scheme 7).

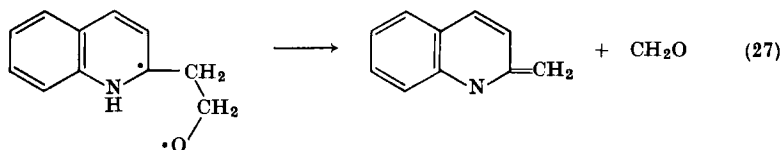


SCHEME 7

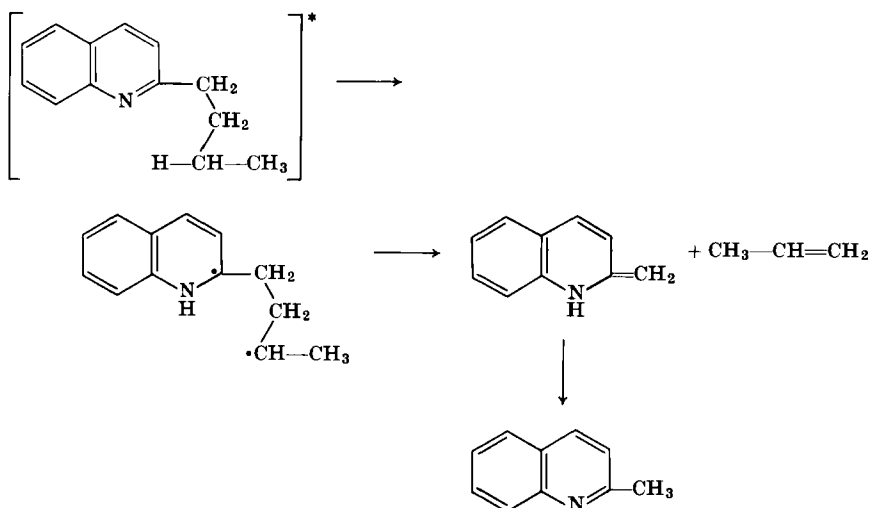
The ease of abstraction of hydrogen in the α -position of alcohols and amines is due to the electrophilic character of the abstracting species (the excited heteroaromatic base, particularly if it is protonated).

Analogous processes, in which hydrogen abstraction takes place intramolecularly, lead to fragmentation of the alkyl derivatives. Thus, the irradiation of 2-*n*-butylquinoline resulted in 45% conversion to 2-methylquinoline and propylene³⁹ (Scheme 8).

Irradiation of 2-(2-hydroxyethyl)quinoline resulted in 73% conversion into 2-methylquinoline and formaldehyde.³⁹ In this case the abstraction of H from OH must occur if the reaction is to be similarly described [Eq. (27)].



³⁹ F. R. Stermitz and C. C. Wei, *J. Amer. Chem. Soc.* **91**, 3103 (1969).



SCHEME 8

Although this process is unusual, a similar one has been suggested for a 9-substituted isoalloxazine derivative where $\text{C}=\text{N}$ photoreactivity is also involved.⁴⁰ Distinction between the above reaction and abstraction through a disfavored five-membered transition state (but from a far more reactive $\text{—CH}_2\text{OH}$) has also been made on the basis of deuterium isotope studies.

Photochemical processes can also lead to *trans*-alkylation. Irradiation of papaverine in methanol or ethanol resulted in 1-methyl- or 1-ethyl-6,7-dimethoxyisoquinoline, the formation of which was interpreted as in Scheme 9.⁴¹

2. Substituent Effects

The homolytic alkylation of protonated heteroaromatic bases is characterized by a very high selectivity (Table II).

The fact that such selectivity was not found with homolytic alkylation of nonprotonated heteroaromatics (Table I) or with homocyclic aromatics indicates that polar factors play a major role in the reactivity of alkyl radicals with protonated bases. These effects were determined by the study of the relative reaction rates in the alkylation of 4-substituted pyridines in acidic medium.¹⁶ The results obtained with methyl, *n*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, and benzyl radicals are summarized in Table III.

⁴⁰ W. M. Moore and C. Baylor, *J. Amer. Chem. Soc.* **88**, 5677 (1966).

⁴¹ F. R. Stermitz, R. Pua, and D. E. Nicodem, *J. Org. Chem.* **33**, 1136 (1968).

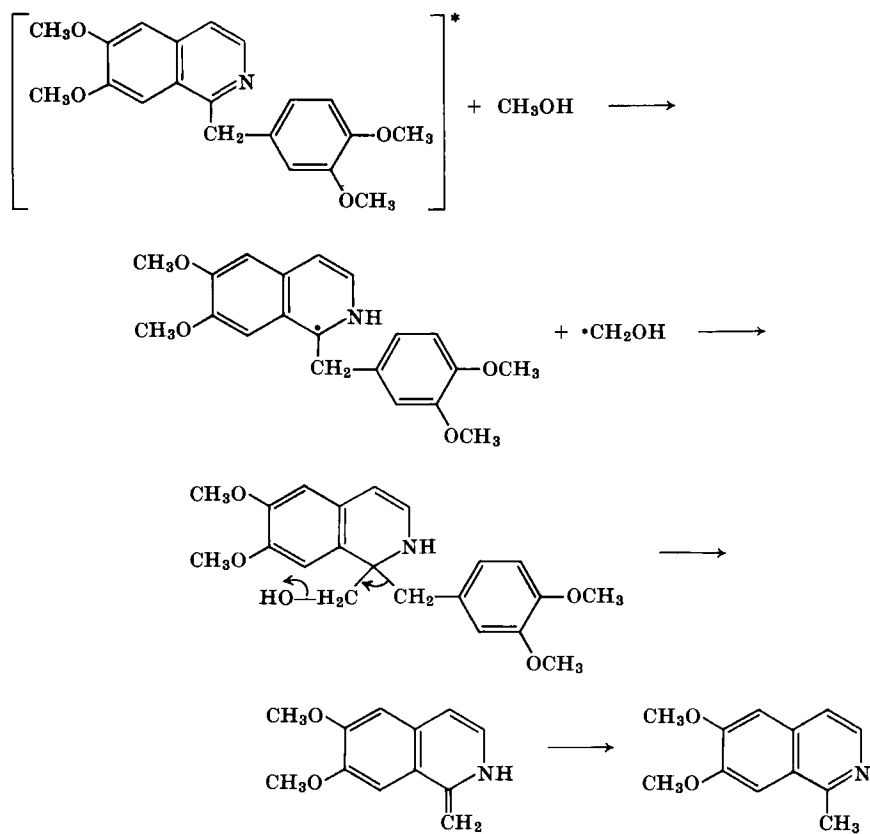


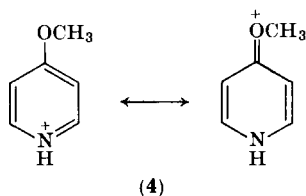
TABLE III

RELATIVE RATES IN THE HOMOLYTIC ALKYLATION OF PROTONATED 4-X-PYRIDINES

X	K_X/K_H^{16}					K_X/K_{Cl}^{42}
	Me	<i>n</i> -Pr	<i>n</i> -Bu	sec-Bu	<i>t</i> -Bu	Benzyl
CN	12.45	19.70	20.30	259.00	1890	233.50
COCH ₃	3.60	5.57	5.60	55.60	144	11.50
Cl	2.38	—	—	—	11.12	1.
H	1	1	1	1	1	—
CH ₃	0.53	0.35	0.32	0.28	0.15	—
OCH ₃	0.27	0.12	0.10	0.02	0.0054	—

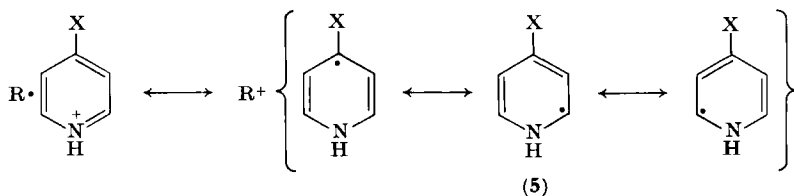
These results clearly show that on the basis of orientation and reactivity all the alkyl radicals have a net nucleophilic character and that this character gradually increases from methyl to primary, secondary, tertiary alkyl and benzyl radicals. A very striking feature is the selectivity shown by the *t*-butyl and the benzyl radicals. The results with the benzyl radical⁴² are incomplete because only traces of benzyl derivatives are formed in the absence of electron-withdrawing groups in the pyridine ring; in these cases the benzyl radical is partly dimerized and partly oxidized rather than attacking the pyridine ring.

A Hammett correlation was not observed, due to enhanced conjugation (4) between the electron-releasing groups and the protonated heterocyclic nitrogen.⁴³



The good correlation (Fig. 2) observed between the relative rates and the chemical shifts of the protons in position 2 of the protonated pyridines indicates that the major factor controlling both the relative shielding of the hydrogen nuclei in the position meta to the substituent and the chemical reactivity is the electron density in position 2 of the unperturbed ground-state molecule.

This high sensitivity to polar effects of the homolytic alkylation of protonated heteroaromatic bases has been interpreted in terms of the transition state.¹⁶ This would be similar to a π -complex in which an enhanced contribution of polar forms (5) would explain the high sensitivity to polar influence.



⁴² Unpublished results.

⁴³ M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron* **19**, 345 (1963).

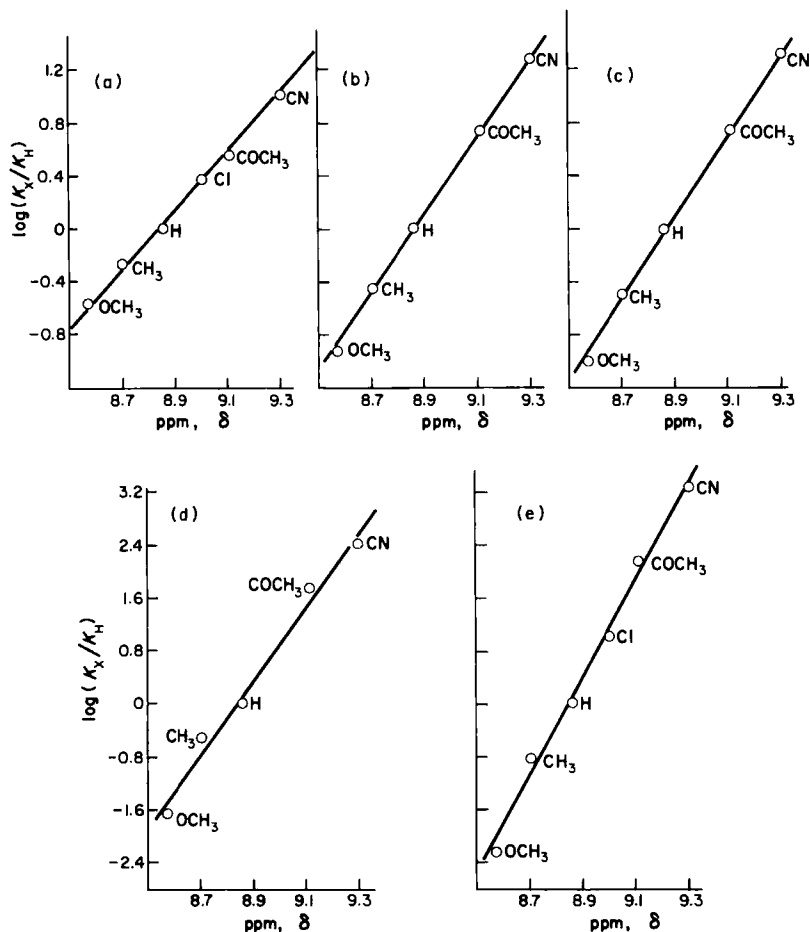


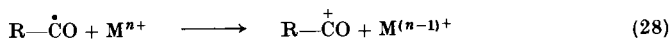
FIG. 2. Correlation of relative rates by chemical shifts of α -protons in protonated 4-X-pyridines, by methyl (a), *n*-propyl (b), *n*-butyl (c), *sec*-butyl (d), and *t*-butyl (e) radicals.¹⁶

III. Acylation

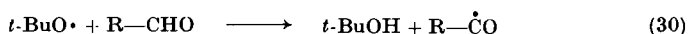
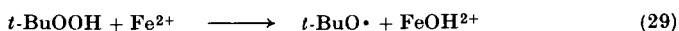
A. SOURCES OF ACYL RADICALS

Two sources of acyl radicals have proved to be useful for the homolytic acylation of protonated heteroaromatic bases: the oxidation of aldehydes and the oxidative decarboxylation of α -keto acids. The oxidation

of aldehydes with various agents takes place through acyl radicals. These are easily oxidized to carboxylic acids and cannot always be used successfully for homolytic acylation, especially if oxidizing salts of high oxidation-reduction potentials (Ce^{IV} , Cr^{VI} , Mn^{VII}) are involved [Eq. (28)].

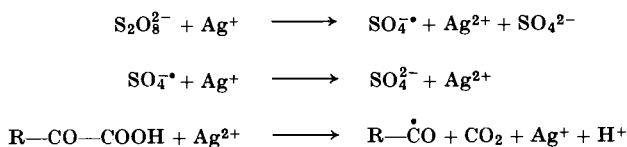


Good results have been obtained by hydrogen abstraction from aldehydes by the redox system *t*-BuOOH/ Fe^{2+} ⁴⁴ [Eqs. (29), (30)].



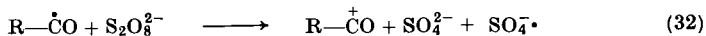
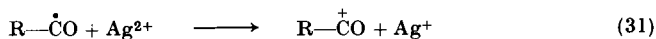
Also in this case the acyl radical can be oxidized by the ferric salt, but in the presence of protonated heteroaromatic bases the aromatic attack successfully competes with the oxidation. The process has great versatility and can be carried out with a large variety of aldehydes (aliphatic, α,β -unsaturated, aromatic, and heteroaromatic).

Acyl radicals have been obtained from α -keto acids by silver-catalyzed decarboxylation with peroxydisulfate. Decarboxylation takes place easily and can be interpreted according to Scheme 10.



SCHEME 10

The acyl radicals attack the protonated heteroaromatic bases with good results,⁴⁵ although the oxidizing medium can lead to the competitive processes of Eqs. (31) and (32).



The possibility of using other sources of acyl radicals, such as tin hydrides and acyl chlorides, is complicated by the fact that homolytic acylation requires an oxidizing medium for the rearomatization of the

⁴⁴ T. Caronna, G. P. Gardini, and F. Minisci, *Chem. Commun.*, 201 (1969).

⁴⁵ T. Caronna, G. Fronza, F. Minisci, and O. Porta, *J. Chem. Soc., Perkin Trans. II*, 2035 (1972).

σ -complex arising from the attack of the acyl radical on the heteroaromatic. Thus using a metal salt such as Ti^{3+} , more reducing than Fe^{2+} in the redox system, with *t*-BuOOH, the σ -complex can be reduced to a dihydro derivative.

B. PRODUCTS OF ACYLATION

The synthetic interest in homolytic acylation is connected with the following aspects:

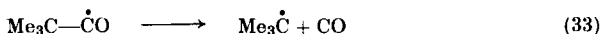
(a) A large variety of heteroaromatic bases and acyl radicals can be used.

(b) The experimental conditions are very simple; the reaction is carried out in aqueous solutions of the salts of the heteroaromatic bases at room temperature.

(c) The selectivity of attack is complete: The reaction proceeds appreciably only at positions of adequate reactivity (α or γ to the heterocyclic nitrogen) and does not normally lead to secondary products; therefore yields based on converted substrates are usually quantitative.

(d) Electrophilic acylation does not usually work with heteroaromatic bases and, in any case, would yield substituent orientations opposite to those found in homolytic acylation. The direct homolytic acylation has no alternative in other synthetic methods. The reaction has been successfully accomplished only in the heteroaromatic series and is unknown in the homocyclic aromatic series. The synthetic interest is shown by the results of Table IV.

The high reactivity of protonated heteroaromatic bases towards acyl radicals is shown by the success of the reaction with the pivaloyl radical, which usually undergoes rapid decarbonylation [Eq. (33)].



Protonated heteroaromatic bases are therefore more reactive than simple olefins toward acyl radicals. The radical addition of pivalaldehyde to olefins is, in fact, characterized by a radical chain, whose propagation is determined by decarbonylation of the pivaloyl radical and addition of *t*-butyl radical to the olefin.⁴⁶ The synthetic interest is great in the case of substrates with only one reactive position, such as benzothiazole,²¹

⁴⁶ E. C. Ladd and L. Y. Kiley U.S. Patent 2,552,980 (1951); *Chem. Abstr.* **45**, 9554i (1951).

TABLE IV
HOMOLYTIC ACYLATION OF HETEROCYCLIC COMPOUNDS

Heterocyclic compound	Radical source	Position of substitution	Yield ^a (%)	Ref.
Quinoxaline	MeCHO	2	70	46, 47
	EtCHO	2	73	46, 47
	<i>i</i> -PrCHO	2	46	46, 47
	<i>t</i> -BuCHO	2	62	46, 47
	2-Furaldehyde	2	51	46, 47
	MeCH=CHCHO	2	45	46, 47
	Ar-CHO ^c	2	52-55	46, 47
	MeCOCOOH	2	42	44, 45
Benzothiazole	MeCHO	2	65	36, 21
	MeCOCOOH	2	41	44, 45
	EtCHO	2	69	36, 21
	Ar-CHO ^c	2	55-80	36, 21
	2-Furaldehyde	2	79	36
	<i>t</i> -BuCHO	2	—	36, 21
6-Nitrobenzo-thiazole	MeCHO	2	—	36, 21
6-Chlorobenzo-thiazole	MeCHO	2	—	36, 21
4-Cyanopyridine	MeCOCOOH	2	—	45, 17
	EtCHO	2	57	44, 45
4-Acetylpyridine	MeCOCOOH	2	—	45, 17
4-Methylpyridine	MeCHO	2	—	45, 17
Pyrazine	MeCHO	2,5	30 ^b	44, 45
	EtCHO	2,5	47 ^b	44, 45
	Ar-CHO ^c	2,5	30-40 ^b	44, 45
Quinoline	MeCHO	2 and 4 (20); 2,4(80)	77	43, 44
	MeCOCOOH	2(22); 4(25); 2,4(53)	53	44, 45
	EtCHO	2,4	40 ^b	44, 45
	Ar-CHO ^c	2,4	26-69 ^b	44, 45
	PhCOCOOH	2,4	40 ^b	44, 45
	MeCHO	2	93	44, 45
4-Cyanoquinoline	Ar-CHO ^c	2	70-90	44, 45
4-Chloroquinoline	MeCHO	2	71	44, 45
	Ar-CHO ^c	2	64-70	44, 45
2-Cyanoquinoline	MeCHO	4	90	44, 45
	PhCHO	4	70	44, 45
2-Methylquinoline	MeCOCOOH	4	40	44, 45
2-Carboxyethyl-quinoline	MeCHO	4	79	44, 45
	PhCHO	4	70	44, 45

(continued)

TABLE IV—*continued*

Heterocyclic compound	Radical source	Position of substitution	Yield ^a (%)	Ref.
2-Methoxyquinoline	PhCHO	4	35	44, 45
	MeCHO	4	75	44, 45
2-Chloroquinoline	MeCHO	4	47	44, 45
	EtCHO	4	52	44, 45
	PhCHO	4	80	44, 45
Acridine	MeCHO	9-Acyl(50); 9-Acyl-9,10-dihydro (50)	30	44, 45
	EtCHO	9-Acyl(50); 9-Acyl-9,10-dihydro (50)	76	44, 45
	EtCHO	9-Acyl-9,10-dihydro	51	44, 45
	PhCHO	9	54	44, 45
	MeCHO	9	62	44, 45
	PhCHO	9	50	44, 45

^a Based on the used heterocyclic compound; conversions are generally not quantitative.

^b The monoacyl derivatives are neglected.

^c Ar = Phenyl and ortho-, meta-, and para-substituted phenyl by Me, OMe, NMe₂, Cl, OH.

quinoxaline,⁴⁷ acridine, 2- and 4-substituted quinolines, and phenanthridine,⁴⁵ and it is possible to obtain very high conversions without formation of polysubstituted products.

Two synthetic aspects emphasize the importance of the polar factor in homolytic acylation. High yields are obtained with substrates containing electron-withdrawing substituents (CN, COOR, COR) in the heteroaromatic ring. The quantitative study¹⁷ of the substituent effect has confirmed the strong influence of the polar characteristics of the substituents on the acylation rates. This is also supported by the behavior of heteroaromatics, such as quinoline or pyrazine, with more reactive positions. In these cases the introduction of an acyl group activates the heteroaromatic ring toward further acylation so that diacylation occurs even with low conversion ratios. The behavior of homolytic alkylation and acylation reactions of protonated heteroaromatic bases is therefore opposite to that of electrophilic alkylation–acylation reactions of homocyclic aromatics. The alkyl groups deactivate the heteroaromatic ring toward further alkylation, so that it is relatively easy to obtain monosubstitution, with partial conversion, contrary to what occurs in acylation. From the synthetic point of view this means that it is easy, for

⁴⁷ G. P. Gardini and F. Minisci, *J. Chem. Soc. C*, 929 (1970).

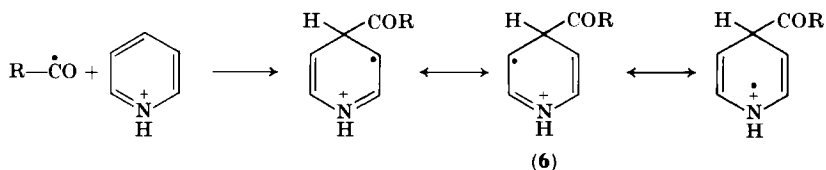
example, with quinoline and pyrazine, to obtain diacyl derivatives by using an excess of acylating agent, while the monoacyl derivatives prevail only at very low conversion ratios. The activating influence of the acyl groups is exemplified in the fact that 4-acetylpyridine was found to be 20 times more reactive than 4-methylpyridine.

It is possible to obtain selective monoacylation even if the heteroaromatic base has more free reactive positions, by taking advantage of the protonation equilibria of the starting base and the reaction products. Thus with 4-cyanopyridine, which has two free reactive positions, the introduction of an acyl group in position 2 decreases the basic character and therefore allows selective monoacylation by the precipitation of the unprotonated reaction product.

With acridine, owing to the greater difficulty of rearomatization, it was possible to obtain the 9-acyl-9,10-dihydro derivatives, particularly by using the redox system $t\text{-BuOOH/Ti}^{3+}$.

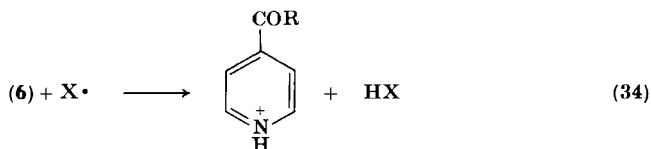
C. MECHANISM OF ACYLATION

Two steps must be considered in the mechanism of homolytic acylation, in addition to the formation of the acyl radical. The first fits in with the generally accepted mechanism of homolytic aromatic substitution, that is, the addition of the acyl radical to the aromatic nucleus to give an adduct in which the unpaired electron is delocalized over the residual heteroaromatic system (σ -complex **6**).

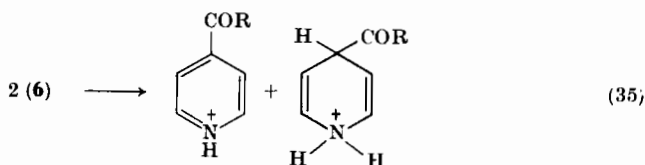


The final step, rearomatization of the σ -complex, can take place through several paths:

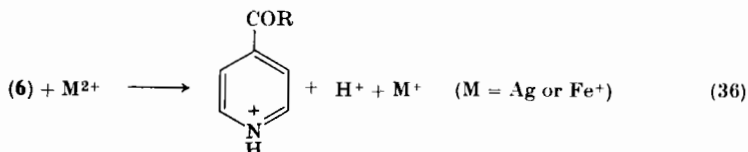
(a) Hydrogen abstraction from the σ -complex by an intermediate radical $\text{X}\cdot$ ($\text{R}-\text{O}\cdot$, $\text{R}-\text{COO}\cdot$, etc.) [Eq. (34)].



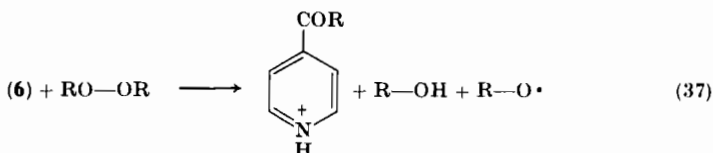
(b) Disproportionation of the σ -complex [Eq. (35)].



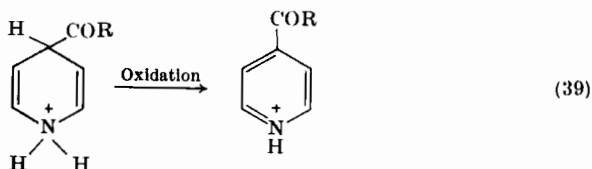
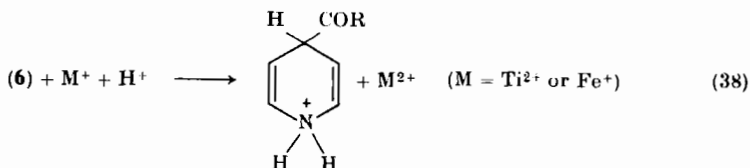
(c) Oxidation of the σ -complex by electron transfer [Eq. (36)].



(d) Oxidation of the σ -complex by induced decomposition of the peroxide acting as source of radicals [Eq. (37)].



(e) Reduction of the σ -complex, followed by oxidation of the dihydro derivative [Eqs. (38), (39)].



This last path has experimental support in the case of the reaction with acridine in the isolation of 9-acyl-9,10-dihydro derivatives.⁴⁵ This behavior can be correlated with the fact that the protonation of the heterocyclic nitrogen and the presence of an electron-withdrawing group (R-CO) causes a relatively high ionization potential of the σ -complex

and so an easier reduction. Probably more processes take part in the rearomatization of the σ -complex; however, this step is mainly determined by the nature of the radical source.

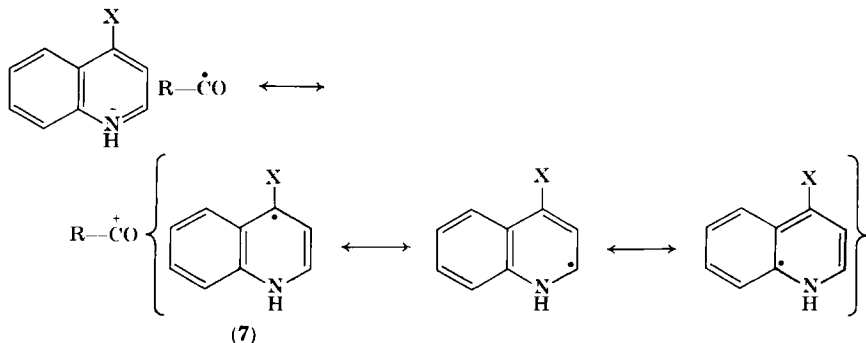
D. ISOMER DISTRIBUTION

The homolytic acylation of protonated heteroaromatic bases is, as with alkylation, characterized by high selectivity. Only the positions α and γ to the heterocyclic nitrogen are attacked. Attack in the β -position or in the benzene ring of polynuclear heteroaromatics has never been observed, even after careful GLC analysis of the reaction products. Quinoline is attacked only in positions 2 and 4; the ratio 4-acyl- to 2-acylquinoline was 1.3 with the acetyl radical from acetaldehyde, 1.7 with the acetyl radical from pyruvic acid, and 2.8 with the benzoyl radical from benzaldehyde.

E. SUBSTITUENT EFFECTS

The high selectivity of homolytic acylation of protonated heteroaromatic bases and the fact that under the same experimental conditions homocyclic substrates (benzene, anisole, nitrobenzene, protonated aniline, and *N,N*-dimethylaniline) are not attacked, indicate that polar effects play a dominant role. Only aromatic substrates with very strong electron-deficient character give rise to significant homolytic acylation.

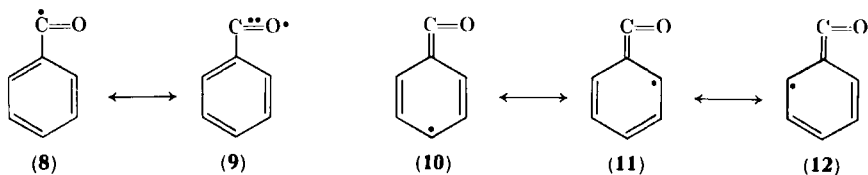
A study¹⁷ of substituent effects in the homolytic acylation of 2- and 4-substituted quinolines with acetyl and benzoyl radicals has confirmed this character of the reaction. The benzoyl radical shows a higher nucleophilic character than the acetyl. This has been explained by the fact that the polar character originates in the contribution of the polar form (7) in the transition state.



The higher stability of the benzoyl cation agrees with the higher sensitivity to polar effects of the corresponding radical.

Also, the influence of substituents in the meta and para positions of the benzoyl radical is in accordance with the polar character of the substituent. The rates for 4-cyanoquinoline relative to 4-chloroquinoline with meta- and para-substituted benzoyl radicals were obtained. Plots of $\log k_{\text{CN}}/k_{\text{Cl}}$ vs. σ of the substituents in the benzoyl radical gave a Hammett correlation; ρ was found to be -0.49 , implying that the effect of the substituent is small, much smaller than the effect of the substituents in the heteroaromatic substrate.

Comparison with the alkyl radicals shows that the selectivity of all the acyl radicals investigated is included between those of a primary and a secondary alkyl radical. A peculiar characteristic of the acyl radicals is therefore that a change in structure of the radical has only a small effect on its polar character and selectivity; this is also clearly shown by the low value of ρ mentioned earlier. This is in contrast with the alkyl radicals, in which the change in structure can cause a very large change in the nucleophilic character. This can be connected with the fact that the acyl radicals are of the σ -type and the alkyl radicals are of the π -type. Thermochemical⁴⁸ and ESR⁴⁹ data suggest that the stabilization of the benzoyl radical (**8**) is determined only by conjugation with the lone-pair electrons of the oxygen atom (structure **9**) and not by conjugation with the phenyl ring (structures **10**, **11**, and **12**).



Thus acyl radicals are relatively insensitive, both as regards stability and reactivity, to substitution. The polar character and the consequent selectivity is therefore mainly determined by the nature of the $-\dot{\text{C}}=\text{O}$ group.

Also, the results of the substituent effects in homolytic acylation of protonated heteroaromatic bases must be connected, as for homolytic alkylation, with the polar characteristics of the acyl radicals and the aromatic substrates, but not with the stabilization of the intermediate σ -complexes.

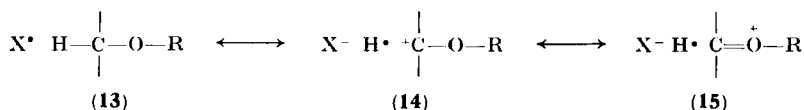
⁴⁸ R. K. Solly and S. W. Benson, *J. Amer. Chem. Soc.* **93**, 1592 (1971).

⁴⁹ P. J. Krusic and T. A. Rettig, *J. Amer. Chem. Soc.* **92**, 722 (1970).

IV. α -Oxyalkylation

A. INTRODUCTION

Hydrogen abstraction from a position α to the oxygen of alcohols and ethers provides a simple route to α -oxyalkyl radicals. Resonance stabilization and polar factors have been used to explain the ease of radical attack on these substrates. Recent studies appear to exclude the possibility that the oxygen atom in position α to the free C-radical may cause stabilization by resonance.^{50, 51} The ease of hydrogen abstraction would be determined only by polar factors, arising with electrophilic radicals ($X\cdot$) in contributions from the polar forms **13**–**15** to the transition state.

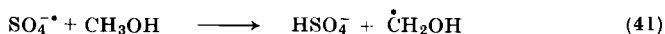


The α -oxyalkyl radicals used for alkylating heteroaromatic bases are formed by the oxidation of alcohols and ethers with a variety of electrophilic radicals or photochemically.

B. OXYALKYLATION BY ALCOHOLS

Oxidation of alcohols with a variety of oxidizing agents leads to α -hydroxyalkyl radicals. These attack protonated heteroaromatic bases only when obtained from methanol or primary alcohols,^{52a, 52b} with secondary alcohols no attack takes place, probably owing to the ease with which such α -hydroxyalkyl radicals are oxidized. (This limitation does not apply to radiation-induced oxyalkylation, see later.)

The best results have been obtained by oxidation with peroxydisulfate. The formation of hydroxyalkyl radicals was originally interpreted according to the mechanism of Eqs. (40) and (41).



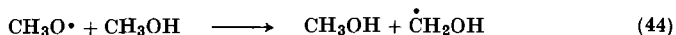
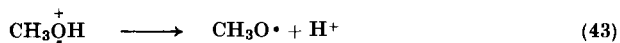
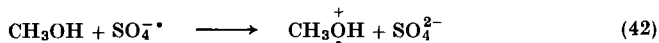
⁵⁰ A. Ohno and Y. Ohnishi, *Tetrahedron Lett.*, 4405 (1968).

⁵¹ J. W. Timberlake and M. L. Hodges, *Tetrahedron Lett.*, 4147 (1970).

^{52a} W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron* **27**, 3655 (1971).

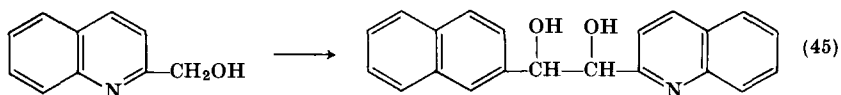
^{52b} M. H. Palmer and P. S. McIntyre, *Tetrahedron Lett.*, 2147 (1968).

Recent studies, however, indicate that the oxidation of methanol takes place by an electron transfer followed by a hydrogen-transfer process⁵³ [Eqs. (42)–(44)].



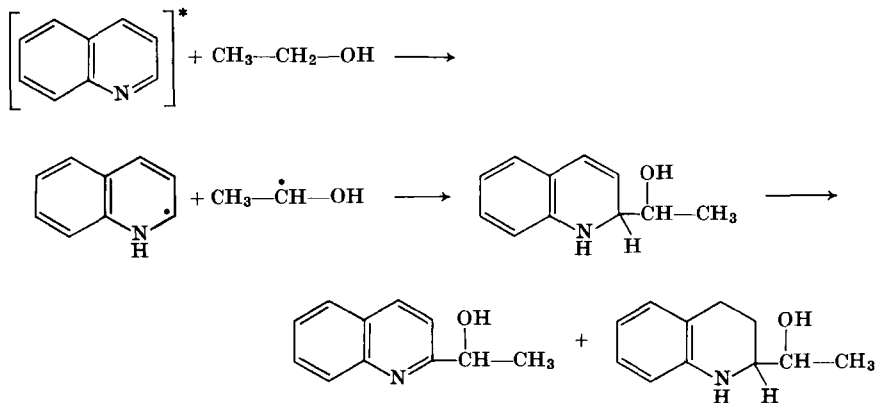
Perborate, peroxydicarbonate, H_2O_2 and Cr^{2+} , $t\text{-BuOOH}$ and Fe^{2+} ,^{52a} and hydroxylamine-*O*-sulfonic acid^{52b} have also been successfully used.

The hydroxymethyl group in a position α to the heterocyclic nitrogen is sensitive to further oxidation and tends to form an oxidative dimer product [Eq. (45)].



The reaction has been studied mainly in the quinoline series. Yields in the range of 30–95% were obtained.⁵²

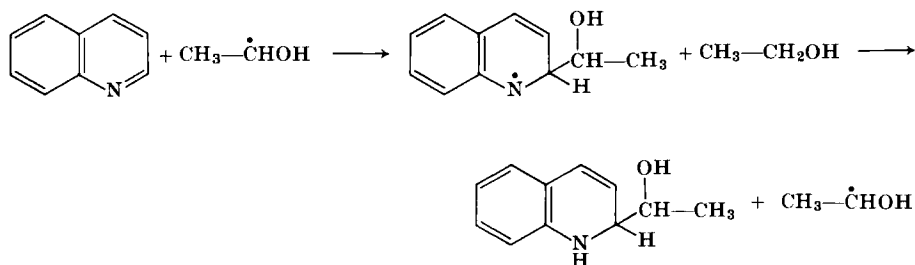
Photochemical α -hydroxyalkylation by alcohols is strictly connected with photochemical alkylation. With quinoline an acidic medium leads to alkylation; hydroxyalkylation takes place with nonprotonated bases. The suggested mechanism is substantially identical for both processes.³⁰ A $\pi \rightarrow \pi^*$ excited state would cause the initial hydrogen abstraction (Scheme 11).



SCHEME 11

⁵³ A. Ledwith, P. J. Russel, and L. H. Sutcliffe, *Chem. Commun.*, 970 (1971).

A chain-type variation, where the alcohol radical formed attacks an unexcited quinoline, has also been suggested (Scheme 12).³⁰



SCHEME 12

This latter variant would resemble α -hydroxyalkylation by oxidizing agents, but would not explain the exclusive attack of position 2.

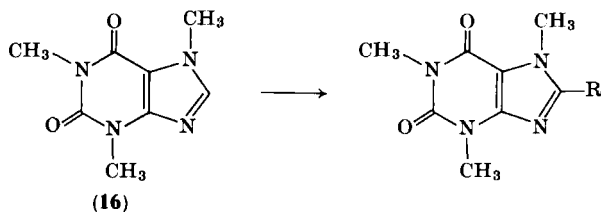
In the case of 8-methylquinoline, the intermediate dihydro derivative yields nearly equal amounts of the two disproportionation products, while with quinoline itself only a trace of the tetrahydro compound was formed.³⁰ In the latter case some other oxidizing agent, perhaps traces of oxygen, must have been involved.

If the mechanism in acid and without acid are the same, one might have expected 4-alkylation under both conditions, and the failure to observe any 4-alkylation when acid is not present is as yet unexplained. Possibly with nonprotonated bases the hydroxyalkylation occurs according to Scheme 11, in which dimerization of two radicals within the solvent cage would lead to attack only at position 2, while in acid the attack could take place, at least in part, according to Scheme 12 but with protonated base, leading to both the isomers (2 and 4), as in the hydroxyalkylation by oxidation of alcohols. The much higher affinity of alkyl radicals toward protonated heteroaromatic bases in comparison with nonprotonated bases would support this interpretation.

Also, the γ -ray-induced reactions in alcohols, which sometimes lead to the same product, support the attack of α -hydroxyalkyl radicals on the unexcited heteroaromatic compound. Yields are particularly interesting in the imidazole series, e.g., with caffeine (16).⁵⁴

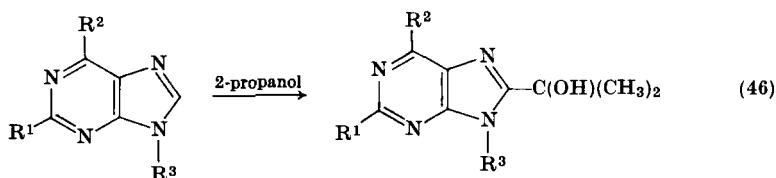
The photochemical and γ -ray-induced reactions of purines and purine nucleosides with 2-propanol lead to substitution of $\text{C}(\text{CH}_3)_2\text{OH}$

⁵⁴ D. Elad, I. Rosenthal, and H. Steinmaus, *Chem. Commun.*, 305 (1969).

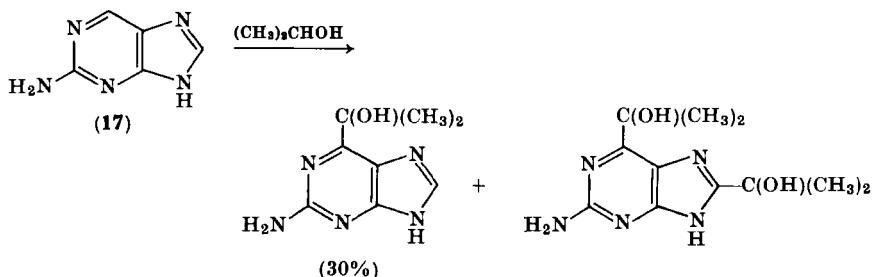


R	Yields (%)	
	UV	γ -Rays
$\text{CH}_3\text{---CH(OH)}$	—	41
$\text{CH}_3\text{---C(OH)---CH}_3$	78	67
$\text{CH}_3\text{---C(OH)---C}_2\text{H}_5$	44	—

at C-8.^{55, 56} The reactions could be induced directly by short-wave-length ultraviolet light or sensitized with acetone when light of longer wavelength (290 nm) was employed, as well as by γ -rays [Eq. (46)].

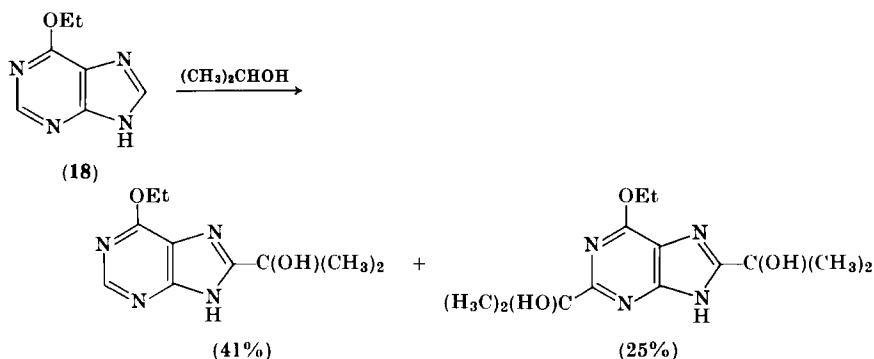


The results⁵⁶ indicate that C-6 in purine and 2-aminopurine (17) is more reactive than C-8 or C-2, while the primary attack at C-8 in adenine and 6-ethoxypurine (18) indicates that C-8 is more reactive than C-2. The order of reactivity toward α -hydroxyalkyl radicals in the purine system is therefore C-6 > C-8 > C-2.

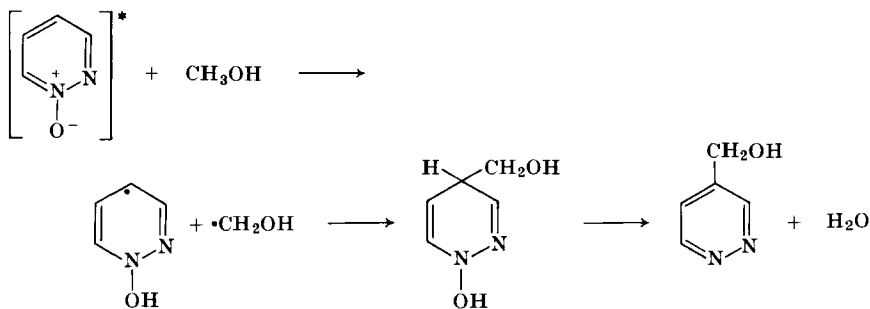


⁵⁵ H. Steinmaus, I. Rosenthal, and D. Elad, *J. Amer. Chem. Soc.* **91**, 4921 (1969).

⁵⁶ H. Steinmaus, I. Rosenthal, and D. Elad, *J. Org. Chem.* **36**, 3594 (1971).



Photochemical hydroxyalkylation has been carried out with pyridines,^{57, 58} quinolines,^{29, 30, 57} isoquinolines,⁵⁷ acridine,⁵⁹ pyridazines,³⁷ pyrimidines,⁶⁰ ethoxyquinolinium salts,⁶¹ and imidazoles.⁵⁴ It also occurs with *N*-oxides; the mechanism of Scheme 13 has been suggested for pyridazine *N*-oxide.⁶²



SCHEME 13

C. OXYALKYLATION BY ETHERS

Hydrogen peroxides, *t*-butyl hydroperoxide, and ammonium peroxydisulfate have been used for the oxyalkylation of protonated heteroaromatic bases by the ethers dioxane, tetrahydrofuran, 1,3-dioxolan,

⁵⁷ M. Natsume and M. Moritaka, *Tetrahedron Lett.*, 4503 (1971).

⁵⁸ R. M. Kellogg, T. J. Van Bergen, and H. Wynberg, *Tetrahedron Lett.*, 5211 (1969).

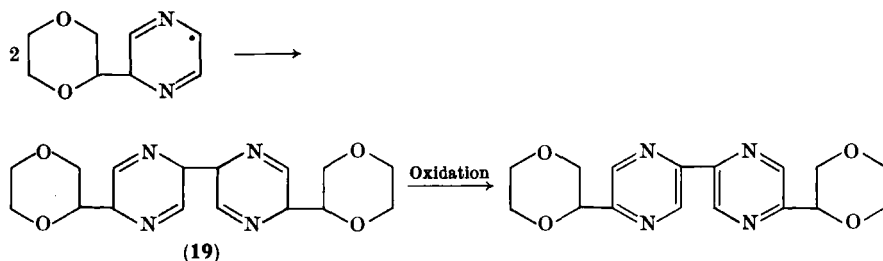
⁵⁹ H. Goth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta* **48**, 1395 (1965).

⁶⁰ E. C. Taylor, Y. Maki, and B. E. Evans, *J. Amer. Chem. Soc.* **91**, 5181 (1969).

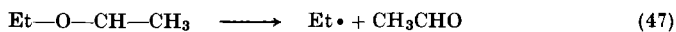
⁶¹ M. Hamana and H. Noda, *Chem. Pharm. Bull.* **17**, 2633 (1969).

⁶² M. Ogata and K. Kano, *Chem. Commun.*, 1176 (1967).

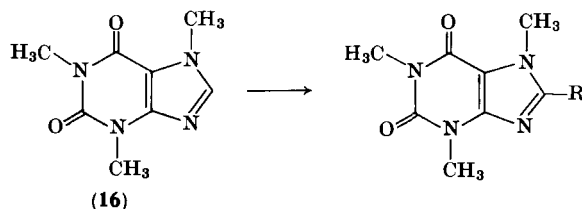
and diethyl ether.⁵² Yields are moderate to good (26–74%). In the case of cyclic ethers the oxyalkyl radicals attack the heterocyclic substrate without undergoing β -scission and the reaction has synthetic interest. With pyrazine and dioxane, in addition to the substitution products, compound **19**, formed via dimerization of the intermediate radical and subsequent oxidation, was also obtained.



Acyclic ethers undergo partial β -scission with formation of carbonyl and alkyl derivatives. Thus with ethyl ether the introduction of the oxyalkyl group is accompanied by appreciable quantities of ethyl and acetyl derivatives, attributed to β -scission of the α -oxyalkyl radical [Eq. (47)].



The ethyl radical directly attacks the heteroaromatic base, while the acetaldehyde acts as a source of acetyl radical. Photochemical oxy-alkylation has also been tried with ethers. The reaction has been successfully carried out with pyridines,⁶³ quinolines,²⁸ isoquinolines,⁵⁷ cinnolines,⁶⁴ and quinoxalines.^{64, 65} Particularly good yields were obtained with caffeine (**16**) (Scheme 14).⁶⁶






⁶³ T. D. Harris, P. L. Kumler, *J. Org. Chem.* **37**, 1830 (1972).

⁶⁴ T. T. Chen, W. Dorscheln, H. Goth, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **51**, 632 (1968).

⁶⁵ A. Castellano, J. P. Catteau, A. Lablache-Combier, B. Planckaert, and G. Allan, *Tetrahedron* **28**, 3511 (1972).

⁶⁶ S. Jerumais and A. Martell, *Can. J. Chem.* **48**, 1716 (1970).

R	Yields (%)
	60-70
	65
	65
$\text{CH}_3-\underset{ }{\text{CH}}-\text{O}-\text{Et}$	50-60

SCHEME 14

D. OXYALKYLATION BY α -OXYACIDS

α -Oxyalkyl radicals are easily obtained by silver-catalyzed decarboxylation of α -hydroxy-, alkoxy-, or phenoxy-carboxylic acids and have been utilized for the oxyalkylation of protonated heteroaromatic bases. High yields of phoxymethyl derivatives of quinoline¹⁴ (100%) and benzimidazole¹⁵ (93%) have been obtained using phenoxyacetic acid; analogously methoxy- and hydroxy-methylations have been obtained by decarboxylation of methoxyacetic and glycolic acids.⁶⁷

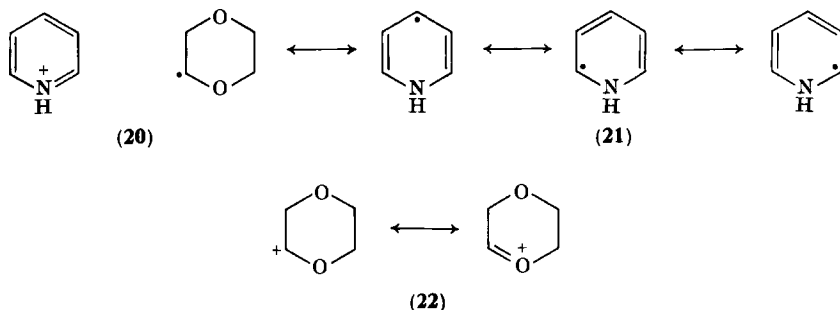
E. QUANTITATIVE STUDIES

The substituent effect in the homolytic oxyalkylation of protonated heteroaromatic bases has been studied by determining the relative reaction rates of the dioxanyl radical with 4-substituted quinolines.⁵² The behavior is similar to that of alkyl and acyl radicals, indicating a net nucleophilic character of the dioxanyl radical. This indicates that the oxygen in the α -position to the C-radical has an electron-releasing effect that counterbalances the inductive electron-withdrawing effect whether of the same oxygen or of that in the β -position. This effect could occur in the ground state of the dioxanyl radical in a similar way as that in which molecular orbital studies show that in alcohols and ethers the oxygen is substantially less negative than in water.⁶⁸ This is primarily associated with back-donation of charge from the π -type lone pair of the oxygen

⁶⁷ C. Amadasi, Ph.D. Thesis, Parma University (1970-1971).

⁶⁸ W. J. Hehre and J. A. Pople, *J. Amer. Chem. Soc.* **92**, 2191 (1970).

into the antibonding orbitals of the adjacent C-H group. This effect would be accentuated in the transition state by the contribution of the polar forms (20-22).

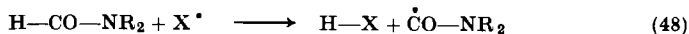


The presence of two oxygen atoms, both influencing the polar character of the dioxanyl radical, makes uncertain any comparison with the reactivity of alkyl radicals. Comparisons with the methoxymethyl ($\text{CH}_3\text{OCH}_2\cdot$) and phenoxymethyl ($\text{C}_6\text{H}_5\text{OCH}_2\cdot$) radicals, obtained by oxidative decarboxylation of the corresponding oxyacetic acids, are more significant. Both these radicals show a greater nucleophilic character than methyl, ethyl, and *n*-propyl radicals in the alkylation of 4-substituted pyridines, indicating that the electron-releasing effect is stronger than the inductive electron-withdrawing effect of the oxygen atom.⁶⁷

V. Amidation

A. SOURCE OF CARBAMOYL RADICALS

Carbamoyl radicals can be easily obtained by hydrogen abstraction from formamides [Eq. (48)].



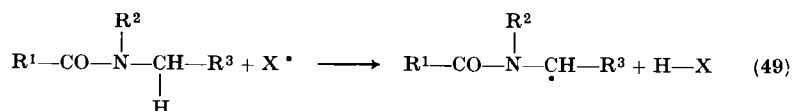
With formamide hydrogen abstraction is quite selective using hydroxy and alkoxy radicals.⁶⁹ With *N*-substituted formamides the site of the hydrogen abstraction depends on the nature of the abstracting species and both the formyl C-H bond and the substituent can be involved.

⁶⁹ F. Minisci, G. P. Gardini, R. Galli, and F. Bertini, *Tetrahedron Lett.*, 15 (1970).

Carbamoyl radicals, like acyl radicals, show a net nucleophilic character which permits the amidation of protonated heteroaromatic bases. Quantitative studies concerning the polar character of the carbamoyl radicals have not yet been published, but the complete selectivity of attack at the α - and γ -positions of protonated heteroaromatic bases indicates a definite nucleophilic character and synthetic value.

B. SOURCES OF α -N-AMIDOALKYL RADICALS

α -N-Amidoalkyl radicals can be obtained by hydrogen abstraction from N-alkylamides [Eq. (49)].



As for ethers and alcohols, the ease of hydrogen abstraction is determined by polar factors when operating with electrophilic radicals (X^\bullet). The polar character is influenced by the same factors as for ethers and alcohols, i.e., a back-donation of charge from nitrogen to the α -C radical accentuates the nucleophilic character. The influence of the abstracting species in the case of dimethylformamide is shown by the results given in Table V, where the attack of carbamoyl and α -amidomethyl radicals

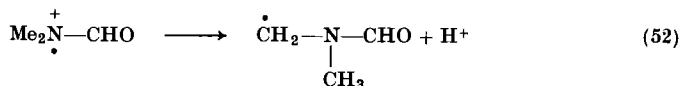
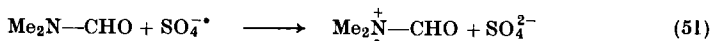
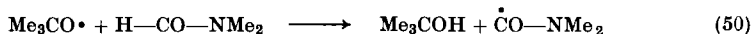
TABLE V

HOMOLYTIC SUBSTITUTION OF THE 2-POSITION OF LEPIDINE BY DIMETHYLFORMAMIDE⁷⁰

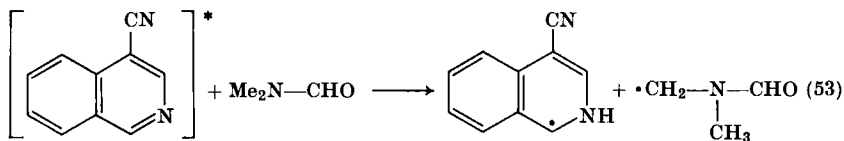
Radical source	Carbamoyl radical (%)	α -Amidomethyl radical (%)
<i>t</i> -BuOOH + Fe ²⁺	97	3
H ₂ O ₂ + Fe ²⁺	85	15
S ₂ O ₈ ²⁻ + Fe ²⁺	2	98
(PhCOO) ₂	40	60

on the 2-position of lepidine is reported with various radical sources. The dramatic difference in selectivity between *t*-butyl hydroperoxide and peroxydisulfate under the same experimental conditions cannot be explained on the basis of the energies of the bonds involved and of the polar characteristics (*t*-BuO \cdot and SO₄⁻ \cdot are both electrophilic radicals).

Two different mechanisms are assumed.^{70a} With *t*-butyl hydroperoxide an actual hydrogen abstraction occurs [Eq. (50)], while with peroxydisulfate the primary process is an electron transfer [Eq. (51)]; deprotonation [Eq. (52)] follows.



The α -amidomethyl radical from dimethylformamide has also been obtained by photochemical processes. The mechanism is identical to that discussed for alcohols and ethers, i.e., hydrogen abstraction by an excited heteroaromatic base [Eq. (53)].⁵⁷



Other amides which have been used for α -amidoalkylation of heteroaromatic bases are *N*-methylformamide,⁷⁰ *N*-methylacetamide,⁷⁰ *N,N*-dimethylacetamide,⁷⁰ *N*-methylpyrrolidone,⁵⁷ *N*-cyclohexylacetamide,^{70b} *N*-acetylpyrrolidine,^{70b} *N,N*-dimethylurea,⁷⁰ and caprolactam.^{70b}

C. PRODUCTS OF AMIDATION

The synthetic interest in direct substitution of protonated heteroaromatic bases by carbamoyl and α -amidoalkyl radicals arises because the reaction is applicable to a variety of heteroaromatic bases having highly reactive nucleophilic positions and because a variety of amides can be used. The selectivity of attack is complete at the α - and γ -positions of the heterocyclic system owing to the nucleophilic character of both carbamoyl and α -amidoalkyl radicals. The results with formamide are shown in Table VI. Quinoline with dimethylformamide gave a variety

^{70a} G. P. Gardini, F. Minisci, G. Palla, A. Arnone, and R. Galli, *Tetrahedron Lett.* **59** (1971).

^{70b} A. Armenzoni, Ph.D. Thesis, Parma University (1970–1971); A. Arnone, M. Cecere, R. Galli, F. Minisci, M. Perchinunno, O. Porta, and G. Gardini, *Gazz. Chim. Ital.* **103**, 13 (1973).

TABLE VI
HOMOLYTIC SUBSTITUTION WITH FORMAMIDE

Heterocyclic compound	Radical source	Position of substitution	Yields (%)	Ref.
4-Cyanopyridine	<i>t</i> -BuOOH	2	97 ^a	66
4-Carboethoxypyridine	<i>t</i> -BuOOH	2	78 ^a	66
4-Acetylpyridine	<i>t</i> -BuOOH	2	46 ^a	66
Quinoline	<i>t</i> -BuOOH	2 and 4	92 ^a	66
4-Methylquinoline	<i>t</i> -BuOOH	2	87 ^a	66
Isoquinoline	<i>t</i> -BuOOH	1	41 ^a	66
Acridine	<i>t</i> -BuOOH	9	100 ^a	66
2-Methylquinoline	<i>t</i> -BuOOH	4	80 ^b	64
Pyridine	<i>t</i> -BuOOH	2 and 4	80 ^b	64
Pyrazine	<i>t</i> -BuOOH	2	80 ^b	64
Quinoxaline	H ₂ O ₂	2	82 ^a	64
Benzimidazole	<i>t</i> -BuOOH	2	60 ^a	22
Benzothiazole	<i>t</i> -BuOOH	2	68 ^a	66
Benzothiazole	H ₂ O ₂	2	62 ^a	66

^a Based on the heterocyclic compound.

^b Based on the converted heterocyclic compound.

of products of amidation and amidomethylation at the 2- and/or 4-position, in proportion strongly dependent on the radical source.⁷⁰ The *N*-methyl- and *N,N*-dimethylamides obtained with various hetero-aromatic bases and methyl and dimethylformamide are shown in Table VII. Table VIII summarizes the results of α -amidoalkylation obtained

TABLE VII
HOMOLYTIC AMIDATION BY MONO- AND DIMETHYLFORMAMIDES^{70b}

Heterocyclic compound	Radical source	Amide ^a	Position of substitution	Yield (%)
4-Acetylpyridine	<i>t</i> -BuOOH + Fe ²⁺	DMF	2	49
4-Cyanopyridine	<i>t</i> -BuOOH + Fe ²⁺	DMF	2	97
4-Carboethoxypyridine	<i>t</i> -BuOOH + Fe ²⁺	DMF	2	36
Benzothiazole	<i>t</i> -BuOOH + Fe ²⁺	DMF	2	61
Lepidine	<i>t</i> -BuOOH + Fe ²⁺	MF	2	45
Quinaldine	<i>t</i> -BuOOH + Fe ²⁺	MF	4	67

^a MF = methylformamide; DMF = dimethylformamide.

TABLE VIII
 HOMOLYTIC α -AMIDOALKYLATION^{70c}

Heterocyclic compound	Radical source	Amide ^a	Position of substitution	Yield (%)
Pyridine	<i>t</i> -Bu ₂ O ₂	DMA	2 and 4	66
Quinoline	S ₂ O ₈ ²⁻	DMA	2 and 4	97
	S ₂ O ₈	MA	2 and 4	86
	<i>t</i> -Bu ₂ O ₂	MA	2 and 4	48
	<i>t</i> -Bu ₂ O ₂	DMA	4	81
Quinaldine	S ₂ O ₈ ²⁻	DMA	4	92
	<i>t</i> -Bu ₂ O ₂	MA	4	56
	<i>t</i> -Bu ₂ O ₂	Cyclohexyl-acetamide	4	36
	S ₂ O ₈ ²⁻	Cyclohexyl-acetamide	4	51
	<i>t</i> -Bu ₂ O ₂	<i>N</i> -Acetyl-piperidine	4	37
	<i>t</i> -Bu ₂ O ₂	MA	2	71
Lepidine	S ₂ O ₈ ²⁻	MA	2	65
	S ₂ O ₈ ²⁻	DMA	2	44
	<i>t</i> -Bu ₂ O ₂	DMA	2	85
	<i>t</i> -Bu ₂ O ₂	<i>N,N</i> -Dimethylurea	2	38
	<i>t</i> -Bu ₂ O ₂	Caprolactam	2	59
Pyrazine	S ₂ O ₈ ²⁻	DMA	2	48
Quinoxaline	<i>t</i> -Bu ₂ O ₂	DMA	2	54
Benzothiazole	<i>t</i> -Bu ₂ O ₂	DMA	2	70
	S ₂ O ₈ ²⁻	DMA	2	66
	S ₂ O ₈ ²⁻	MA	2	9
	<i>t</i> -Bu ₂ O ₂	MA	2	55

^a MA = *N*-methylacetamide; DMA = *N,N*-dimethylacetamide.

using various amides and heteroaromatic bases. In these cases no formyl C-H bond is present, so that amidoalkylation occurs. Even if hydrogen abstraction took place from the α -position to the carbonyl, $\text{>N-CO}-\dot{\text{C}}$, the nucleophilic character of this radical is decreased by the proximity of an electron-withdrawing group (C=O) and the reactivity toward protonated heteroaromatic bases is strongly reduced.

Radicals similar to carbamoyl are the alkoxycarbonyl radicals, RO $\dot{\text{C}}$ O. Also, these radicals were successfully used to carboxylate protonated heteroaromatic bases with good yields and selectivity.^{70c}

^{70c} R. Bernardi, T. Caronna, R. Galli, F. Minisci, and M. Perchinunno, *Tetrahedron Lett.*, 645 (1973).

Useful sources of these radicals were the hydrogen abstraction from alkyl formate and especially the decomposition by ferrous salts of mixtures of hydrogen peroxide and α -keto esters. The alkoxy-carbonyl radicals appear to be less nucleophilic than carbamoyl radicals.

VI. Arylation

A. INTRODUCTION

In the last ten years arylation has been the most studied homolytic aromatic substitution, also in the heteroaromatic series. Numerous data concerning a large variety of heterocycles have permitted the definition of many details for the individual substrates, without adding, however, anything particularly new as regards the general characteristics of the reaction, already outlined in the previous review of Norman and Radda.² These characteristics are substantially the same as those observed in the homocyclic aromatic series, for which comprehensive reviews are available.⁷¹ There is therefore a sharp difference in behavior between arylation and other homolytic substitutions described in the previous sections. These latter have quite different characteristics, and sometimes they are not known, in the homocyclic series.

B. SOURCES OF ARYL RADICALS

The usual sources used for the homolytic aromatic arylation have been utilized also in the heterocyclic series. They are essentially azo- and diazocompounds, aroyl peroxides, and sometimes pyrolysis and photolysis of a variety of aryl derivatives. Most of these radical sources have been described in the previous review concerning this subject,² and in other reviews concerning the general aspects of homolytic aromatic arylation.⁷¹ A new source of aryl radicals is the silver-catalyzed decarboxylation of carboxylic acids by peroxydisulfate, which allows to work in aqueous solution of protonated heteroaromatic bases, as for the alkyl radicals.⁷²

⁷¹ G. H. Williams, "Homolytic Aromatic Substitution." Pergamon, Oxford, 1960; D. H. Hey, *Advan. Free Radical Chem.* **2**, 47 (1967).

⁷² A. Clerici, F. Minisci, and O. Porta, *Gazz. Chim. Ital.* **103**, 171 (1973).

C. PRODUCTS OF ARYLATION

The low selectivity affects the synthetic interest of homolytic arylation from two points of view. The first concerns the position of substitution; generally all the free positions are substituted, giving very complex mixtures of isomers. Thus, for example, quinoline gives all the seven possible isomers in appreciable amounts.⁷³ This is in contrast to all the homolytic substitutions described in the previous sections, which lead to exclusive attack at the 2- and 4-positions. The other aspect concerns the conversions of the heterocyclic compounds, which are always very low, usually lower than 1%. If the conversions are high, the mixture of the reaction products becomes much more complex. Thus with quinoline it can be easily foreseen from the partial rate factors (Table IX) that not only all the possible 21 diphenylquinoline isomers, but also

TABLE IX

RELATIVE RATES AND PARTIAL RATE FACTORS FOR HOMOLYTIC PHENYLATION OF PYRIDINE, QUINOLINE, AND BENZOTHAIAZOLE

Heterocyclic compound	Radical source	Relative rates	Partial rate factors								Ref.
			2	3	4	5	6	7	8		
Pyridine	Benzene diazonium salt	1.14	1.8	1	1.2	—	—	—	—	100, 102	
Quinoline	Benzoyl peroxide	5.0	3.3	1.8	5.4	6.6	1.5	1.6	9.6	73	
Benzothiazole	Benzoyl peroxide	3.0	6.8	—	4.4	—	—	3.0	—	99	

the 21 phenylation products of the first phenyl group introduced, could be formed, in all 42 compounds. Comparing this situation with that of the other homolytic substitutions described above, which all lead to a sole product of disubstitution (isomer 2,4), even with complete conversion of quinoline, the great difference between these processes from a synthetic point of view is quite obvious. Analogously, phenylation of 2-phenylthiazole leads to all the possible isomers in the heterocyclic ring and in the benzene ring [2,4-diphenyl (7.5%), 2,5-diphenyl (42%), 2-(*o*-biphenyl) (30%), 2-(*m*-biphenyl) (7.5%), 2-(*p*-biphenyl) (13%)].⁷⁴

⁷³ G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 2612 (1971).

⁷⁴ G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 4514 (1967).

Low selectivity is the most qualifying aspect of homolytic arylation. Therefore most of the studies were carried out not in order to develop useful processes from the synthetic point of view, but in order to study the reactivity of the heteroaromatic substrates toward the aryl radicals.

In the last ten years extensive studies of homolytic arylation have been made in the following heterocyclic series: furan,⁷⁵⁻⁷⁷ thiophene,⁷⁸⁻⁸⁵ thiazole,^{74, 86-97} isothiazole,⁹⁸⁻¹⁰⁰ pyrazole,^{88, 92, 98, 99} imidazole,¹⁰⁰

- ⁷⁵ O. C. Ayres and J. R. Smith, *J. Chem. Soc. C*, 2737 (1968).
⁷⁶ L. Benati, M. LaBarba, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 1253 (1969).
⁷⁷ K. E. Kolb and W. A. Black, *Chem. Commun.*, 1119 (1969).
⁷⁸ C. E. Griffin and K. R. Martin, *Chem. Commun.*, 154 (1965).
⁷⁹ C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 1251 (1969).
⁸⁰ E. K. Fields and S. Meyerson, *J. Org. Chem.* **35**, 67 (1970).
⁸¹ C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 1683 (1970).
⁸² G. Vernin, G. Loridan, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 2705 (1970).
⁸³ P. Spagnolo, L. Testaferri, M. Tiecco, and G. Martelli, *J. Chem. Soc. Perkin Trans. I*, 93 (1972).
⁸⁴ P. Spagnolo, M. Tiecco, A. Tundo, and G. Martelli, *J. Chem. Soc. Perkin Trans. I*, 556 (1972).
⁸⁵ C. Camaggi, G. De Luca, and A. Tundo, *J. Chem. Soc. Perkin Trans. 2*, 412 (1972).
⁸⁶ J. Vitry-Raymond and J. Metzger, *Bull. Soc. Chim. Fr.*, 1784 (1963).
⁸⁷ G. Vernin and J. Metzger, *Bull. Soc. Chim. Fr.*, 2504 (1963).
⁸⁸ H. J. M. Dou and B. M. Lynch, *Tetrahedron Lett.*, 897 (1965).
⁸⁹ H. J. M. Dou and B. M. Lynch, *C.R. Acad. Sci., Ser. C*, **262**, 687 (1966).
⁹⁰ G. Vernin, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci., Ser. C* **263**, 1310 (1966).
⁹¹ H. J. M. Dou, G. Vernin, and J. Metzger, *C.R. Acad. Sci., Ser. C* **263**, 1243 (1966).
⁹² H. J. M. Dou and B. M. Lynch, *Bull. Soc. Chim. Fr.*, 3915 (1966).
⁹³ G. Vernin, *C.R. Acad. Sci., Ser. C* **265**, 744 (1967).
⁹⁴ G. Vernin, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci., Ser. C* **265**, 744 (1967).
⁹⁵ G. Vernin, H. J. M. Dou, and J. Metzger, *Tetrahedron Lett.* 2223 (1967).
⁹⁶ G. Vernin and H. J. M. Dou, *C.R. Acad. Sci., Ser. C* **266**, 822 (1968).
⁹⁷ G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 3280 (1968).
⁹⁸ B. M. Lynch and M. A. Khan, *Can. J. Chem.* **41**, 2086 (1963); F. Hubenett and H. Hofmann, *Angew. Chem. Int. Ed. Engl.* **2**, 325 (1963).
⁹⁹ B. M. Lynch and H. S. Chang, *Tetrahedron Lett.*, 617 (1964); H. J. M. Dou, J. C. Poite, G. Vernin, and J. Metzger, *Tetrahedron Lett.*, 779 (1969).
¹⁰⁰ B. M. Lynch and H. S. Chang, *Tetrahedron Lett.*, 2965 (1964); J. C. Poite, G. Vernin, G. Loridan, H. J. M. Dou, and J. Metzger, *Tetrahedron Lett.*, 3912 (1969).

benzothiazole,¹⁰¹⁻¹⁰³ pyridine,^{88, 92, 104-123} pyridazine,^{92, 124} quino-
line,^{73, 82, 92, 124} isoquinoline,^{92, 124} and quinoxaline.^{92, 124}

Of more synthetic interest, at least as regards phenylation, is the reaction of heteroaromatic radicals with benzene. In this case, if the radical source is easily available, it is possible to work with a very large excess of benzene and to obtain complete conversion of the heterocyclic compound into only one phenylated isomer. The method has successfully been used with thienyl¹²⁵⁻¹³⁰ and thiazolyl¹³¹⁻¹³⁴ radicals.

- ¹⁰¹ H. J. M. Dou and B. M. Lynch, *C.R. Acad. Sci., Ser. C* **262**, 1537 (1966).
¹⁰² G. Vernin, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci., Ser. C* **268**, 977 (1969).
¹⁰³ G. Vernin, G. Loridan, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 2705 (1970).
¹⁰⁴ R. A. Abramovitch and J. H. Saha, *Tetrahedron Lett.*, 301 (1963).
¹⁰⁵ D. H. Hey, D. A. Shingleton, and G. H. Williams, *J. Chem. Soc.*, 5612 (1963).
¹⁰⁶ R. A. Abramovitch and J. H. Saha, *J. Chem. Soc.*, 2175 (1964).
¹⁰⁷ R. J. Gritter and A. W. Godfrey, *J. Amer. Chem. Soc.* **86**, 4724 (1964).
¹⁰⁸ J. M. Bonnier and J. Court, *Bull. Soc. Chim. Fr.*, 3310 (1965).
¹⁰⁹ R. A. Abramovitch and J. H. Saha, *Tetrahedron* **21**, 3297 (1965).
¹¹⁰ R. A. Abramovitch and J. H. Saha, *J. Chem. Soc. B*, 733 (1966).
¹¹¹ J. M. Bonnier, J. Court, and M. Gelus, *C.R. Acad. Sci., Ser. C* **263**, 262 (1966).
¹¹² R. A. Abramovitch and J. H. Saha, *Can. J. Chem.* **44**, 1765 (1966).
¹¹³ G. Vernin and H. J. M. Dou, *C.R. Acad. Sci., Ser. C* **265**, 828 (1967).
¹¹⁴ J. M. Bonnier, J. Court, and M. Gelus, *C.R. Acad. Sci., Ser. C* **264**, 1023 (1967).
¹¹⁵ G. Vernin, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci., Ser. C* **264**, 1762 (1967).
¹¹⁶ J. M. Bonnier, J. Court, and T. Fay, *Bull. Soc. Chim. Fr.*, 1204 (1967).
¹¹⁷ G. Vernin, H. J. M. Dou, L. Bouscasse, and J. Metzger, *Bull. Soc. Chim. Fr.*, 3387 (1967).
¹¹⁸ G. Vernin and H. J. M. Dou, *C.R. Acad. Sci., Ser. C* **266**, 924 (1968).
¹¹⁹ H. J. M. Dou, G. Vernin, and J. Metzger, *Tetrahedron Lett.*, 953 (1968).
¹²⁰ J. M. Bonnier, J. Court, and M. Gelus, *Bull. Soc. Chim. Fr.*, 139 (1970).
¹²¹ R. M. Elofson, F. F. Godallah, and K. F. Schulz, *J. Org. Chem.* **36**, 1526 (1971).
¹²² J. M. Bonnier and J. Court, *Bull. Soc. Chim. Fr.*, 1834 (1972).
¹²³ J. Court, S. Vidal, and J. M. Bonnier, *Bull. Soc. Chim. Fr.*, 3107 (1972).
¹²⁴ H. J. M. Dou and B. M. Lynch, *C.R. Acad. Sci., Ser. C* **262**, 1537 (1966).
¹²⁵ W. Wolf and N. Kharash, *J. Org. Chem.* **30**, 2493 (1965).
¹²⁶ L. Benati and M. Tiecco, *Boll. Sci. Fac. Chim. Ind. Bologna* **24**, 45, 225 (1966).
¹²⁷ R. M. Kellog and H. Wynberg, *J. Amer. Chem. Soc.* **89**, 3495 (1967).
¹²⁸ G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 901 (1968).
¹²⁹ L. Benati, G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 472 (1969).
¹³⁰ G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 1413 (1970).
¹³¹ G. Vernin, B. Barre, H. J. M. Dou, and J. Metzger, *C.R. Acad. Sci., Ser. C* **268**, 2025 (1969).

D. QUANTITATIVE STUDIES

The effect of heteroatoms in the aromatic ring on the reactivity toward aryl radicals is usually small. Table X shows the reactivities

TABLE X

RELATIVE RATES AND PARTIAL RATE FACTORS FOR THE HOMOLYTIC PHENYLATION OF FIVE-MEMBERED HETEROCYCLES.

Heterocyclic compound	Source of phenyl radical	Relative rates	Partial rate factors				Ref.
			2	3	4	5	
Furan	Aniline + RONO	11.5	34.5	0.1	—	—	76
Thiophene	Aniline + RONO	2.6	7.3	0.5	—	—	76
Thiazole	Nitrosoacetanilide	1.6	6.2	—	1.0	2.8	93
2-Methylthiazole	Benzoylperoxide	0.6	—	—	1.0	2.4	74
2-Ethylthiazole	Benzoylperoxide	0.6	—	—	1.0	2.4	74
2-Isopropylthiazole	Benzoylperoxide	0.55	—	—	0.9	2.4	74
2- <i>t</i> -Butylthiazole	Benzoylperoxide	0.5	—	—	0.5	2.5	74
4-Methylthiazole	Benzoylperoxide	1.2	2.9	—	—	4.3	74
5-Methylthiazole	Benzoylperoxide	0.8	3.8	—	1.0	—	74
Isothiazole	Benzoylperoxide	0.95	—	2.7	0.5	2.5	96
1-Methylpyrazole	Benzoylperoxide	0.6		0.18	0.03	3.4	95, 96
1-Methylimidazole	Benzoylperoxide	1.2		2.7	0.5	2.5	95, 96

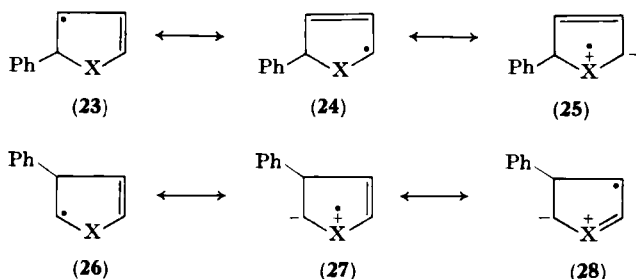
relative to benzene and the partial rate factors for the phenylation of some five-membered heterocycles. The order of magnitude is the same as that of benzene, with the exception of furan, which shows a somewhat higher reactivity. This must be ascribed to the dienic character of the substrate, which also affects the isomer distribution because attack at the

¹³² G. Vernin, R. Jauffred, H. J. M. Dou, and J. Metzger, *J. Chem. Soc. B*, 1678 (1970).

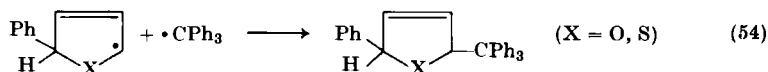
¹³³ G. Vernin, R. Jauffred, C. Ricard, H. J. M. Dou, and J. Metzger, *J. Chem. Soc. Perkin Trans. 2*, 1145 (1972).

¹³⁴ G. Vernin, J. C. Poite, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 3057 (1972).

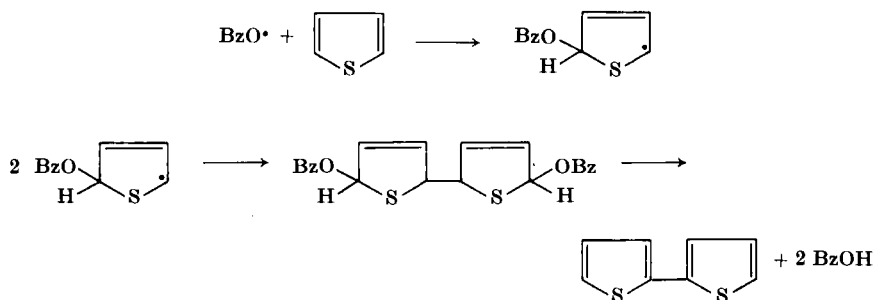
2-position in a transition state similar to a σ -complex leads to an intermediate (allylic-type radical) more stabilized than that arising from attack at position 3 (**23–25**, **26–28**).



The use of phenylazotriphenylmethane as the source of the phenyl radical gave also two stereoisomeric 2,5-dihydro-2-phenyl-5-triphenylmethyl derivatives⁷⁹ [Eq. (54)].



The phenylation of thiophene with benzoyl peroxide gave a considerable amount of 2,2'-dithienyl; one suggested mechanism⁷⁸ involved the formation of 2-thienyl radicals by oxidation, and their subsequent dimerization. More recent studies¹³⁵ indicate that the 2,2'-dithienyl is formed through an initial addition of benzoxy radicals to the thiophene nucleus followed by dimerization of the resulting radical and loss of two molecules of benzoic acid (Scheme 15).

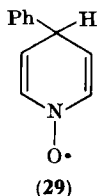


SCHEME 15

Table IX shows the relative reactivities and the partial rate factors for the phenylation of pyridine, quinoline, and benzothiazole, which

¹³⁵ M. Tiecco, personal communication.

indicate low selectivity also for six-membered and bicyclic heteroaromatics. *N*-Oxides of heterocyclic compounds seem to have a higher reactivity; this is shown by the partial rate factors in the phenylation of pyridine *N*-oxide¹²¹ (α 139, β 1.5, γ 31.2) compared with those of pyridine^{104, 106} (α 1.8, β 1.0, γ 1.2). These values agree fairly well with those calculated from the atom localization energies with $\beta_{N-O} = 0.95 \beta$. The effect of the *N*-oxide group is very small in the β -position. This could be ascribed to the small nucleophilic character of the phenyl radical (the same effect observed in acidic medium), and above all to the stability of the σ -complex which has a nitroxide type structure (29).



Substituent effects on the reactivity of the aryl radicals are usually small, for substituents either in the heterocyclic ring or in the aryl radical. The effect of the substituent in the aryl radical depends on the nature of the heterocyclic compound. With electron-rich substrates, such as thiophene, electron-withdrawing groups increase the reactivity, and electron-releasing groups decrease it; a Hammett correlation is observed with a ρ value of 0.22.⁸¹ The opposite occurs with electron-deficient substrates, such as pyridine.^{106, 110} Protonation of the heteroaromatic bases causes some increase in reactivity of the α - and γ -positions in homolytic phenylation. The phenomenon was observed with pyridine,^{72, 113, 115, 120, 122, 123, 136} quinoline,⁷³ thiazoles,⁷⁴ benzothiazole,^{101, 103} and isothiazole.¹⁰⁰ Also, the increase of the decomposition rate of benzoyl peroxide on going from nonprotonated to protonated quinoline was ascribed to a higher affinity of the phenyl radical toward the protonated base with some induced decomposition.⁴ No satisfactory explanation was suggested for this increased reactivity. Some attempts to correlate the reactivity with theoretical indices, such as the free valence number and the atom localization energy, predict the increased reactivity of the 2-position, but not of the 4-position.^{122, 137}

The partial rate factors for phenylation of protonated and nonprotonated 4-substituted pyridines⁷² indicate a small but definite

¹³⁶ J. M. Bonnier and J. Court, *C.R. Acad. Sci., Ser. C* **265**, 133 (1967).

¹³⁷ G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1173 (1972).

nucleophilic character of the phenyl radical. The comparison with the results of alkylations and acylation in which the homolytic substitution occurs exclusively in the 2-position shows the substantial difference in behavior of the phenyl radical, due to its much lower nucleophilic character. This polar character is not sufficient to produce complete selectivity of attack, as in the substitutions described in Sections II-V, but it can explain some increase of reactivity and selectivity in acidic media. The transition state of phenylation in acidic medium would always be similar to a σ -complex, but with more π -character and higher contribution of polar forms in comparison with the phenylation of non-protonated bases and homocyclic aromatics. The different sensitivity to the polar effects of aryl and alkyl radicals has been ascribed to the different transition states¹⁶ and was connected with the fact that the former are radicals of the σ -type and the latter of the π -type.¹⁷

VII. Other Reactions

Electrophilic radicals, such as halogen atoms, hydroxy, alkoxy, and amino radicals, do not seem to have great value in reactions with heterocyclic compounds.

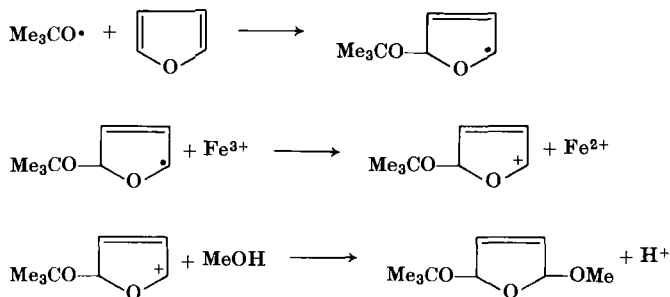
The amino cation radicals, which are of very high synthetic interest in the homocyclic aromatic series,¹ are of less use with heteroaromatic compounds because either the heterocyclic compound is too deactivated or it is unstable in the strongly acidic medium necessary to generate protonated amino radicals. Thus quinoline is not attacked by amino cation radicals because the protonated heterocyclic nitrogen deactivates both rings; with 8-methoxyquinoline, however, the electron-releasing effect of the methoxyl counterbalances the electron-withdrawing effect of the heterocyclic nitrogen and the homolytic amination quantitatively leads to the 5-amino derivative.¹³⁸

Heteroaromatics very reactive toward electrophilic species, such as furan and pyrrole, are not suitable for homolytic aminations owing to their low stability under the reaction conditions. Thiophene, however, can be aminated, leading to 2-dialkylamino derivatives.⁴²

Alkoxy radicals react easily with the furan ring; the initial attack is not followed by rearomatization, but 2,5-dihydro derivatives are formed.¹³⁹ Thus with *t*-BuOOH and Fe²⁺ in methanol the reaction products were interpreted according to Scheme 16.

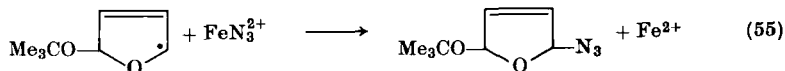
¹³⁸ F. Minisci, R. Galli, M. Cecere, and V. Trabucchi, *Chim. Ind. (Milan)* **48**, 1147 (1966).

¹³⁹ F. Minisci, R. Galli, and M. Cecere, *Gazz. Chim. Ital.* **94**, 67 (1964).

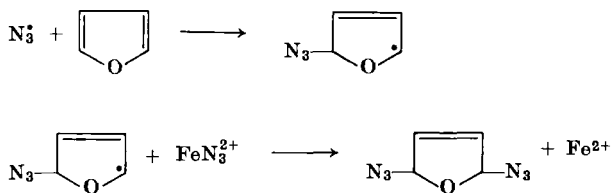


SCHEME 16

In the presence of azide ions the alkoxyazido derivative was obtained [Eq. (55)].



Analogously, the azido radical leads to a 2,5-diazido dihydro derivative¹³⁹ (Scheme 17).



SCHEME 17

The reaction of furan with benzoyl peroxide gave in good yield the *cis*- and *trans*-2,5-dibenzoyloxy-2,5-dihydrofuran.¹⁴⁰ Analogously, the electrolysis of sodium acetate in the presence of furan gave 2,5-diacetoxy-2,5-dihydrofuran.¹⁴¹

The reaction of thiophene with thiyl radicals gave the corresponding 2,5-disubstituted derivatives.¹⁴²

VIII. Conclusions

The most interesting development in the field of homolytic aromatic substitution in recent years is the realization that polar effects in

¹⁴⁰ K. E. Kolb and W. A. Black, *Chem. Commun.*, 1119 (1969).

¹⁴¹ K. E. Kolb and C. L. Wilson, *Chem. Commun.*, 272 (1966).

¹⁴² I. Ya Gol'dfarb, G. P. Pokhil, and L. I. Belen'kii, *Zh. Obshch. Khim.* **37**, 2670 (1967); *Dokl. Akad. Nauk SSSR* **167**, 823 (1966).

several reactions play a role more important than that foreseeable a few years ago. The extent of these effects is determined by both the nature of the free radicals and the reacting substrates, so that strong polar effects were observed not only with strongly polar radicals, but also with moderately polar radicals, such as carbon-free radicals, if the reacting substrate has a marked polar nature.

This awareness in a short time led to new homolytic aromatic substitutions, characterized by high selectivity and versatility. Further developments along these lines can be expected, especially as regards reactions of nucleophilic radicals with protonated heteroaromatic bases, owing to the intrinsic interest of these reactions and to the fact that classical direct ionic substitution (electrophilic and nucleophilic) has several limitations in this class of compound and does not always offer alternative synthetic solutions. Homolytic substitution in heterocyclic compounds can no longer be considered the "Cinderella" of substitution reactions.

Recent Advances in the Chemistry of Dibenzothiophenes

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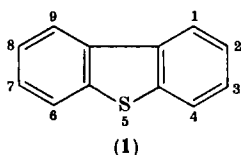
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I. Introduction

This review deals with the chemistry of dibenzothiophene (1) and its derivatives from the beginning of 1952 to December 31, 1970. Although

every effort has been made to include references to all the relevant literature which has appeared in *Chemical Abstracts* up to and including Volume 73, this review is by no means exhaustive in terms of actual compounds described during this period. Rather, we have attempted to focus attention on new synthetic and spectroscopic techniques and the completion of the many series of four, isomeric, *monosubstituted* derivatives. Several papers appearing in 1971 and 1972 have been included, although coverage of this period is not comprehensive. The literature relating to dibenzothiophene prior to 1952 has been covered in detail by Hartough and Meisel¹ and we have arranged the present work as an extension to their monograph.



The currently accepted name for (1) in *Chemical Abstracts* is dibenzothiophene, although biphenylene, diphenylene, or biphenylene sulfide are still used, especially in the Russian literature. Occasionally 9-thiafluorene is used and recently, in one instance, dibenzo[*b,d*]thiophene. An alternative numbering system for (1) is met with on occasions in which C-4 is taken as C-1, as in carbazole. In the absence of molecular diagrams this system must be detected by reference to the chemistry described. For example, in a few dyestuff patents 2,7-diaminodibenzothiophene 5,5-dioxide is referred to and this is obviously the 3,7-diamino compound, also known as benzidine sulfone.

The literature relating to dibenzothiophene falls into three distinct groups. The first, as typified by the work of Gilman and co-workers, is primarily concerned with the exploration and documentation of derivatives of dibenzothiophene. This approach was essentially the overriding theme of the previous review and is now declining. Depletion of high-grade crude oil reserves has forced the petroleum industry to use crude oils having increasingly higher sulfur contents. This has added impetus to several fundamental studies on the nature of the sulfur compounds present in petroleum. The discovery of a large proportion of fused thiophenes, in particular dibenzothiophenes, among the sulfur compounds of such oils has provided the second main area of research. The third area is concerned with the preparation of sulfur isosteres of

¹ H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), p. 226. Wiley (Interscience), New York, 1954.

biologically active compounds. This includes the work of Sawicki on the carcinogenicity of various amine derivatives of dibenzothiophene and the work of Tilak and co-workers on the synthesis of thiophene analogs of several steroids. Much fundamental chemistry of dibenzothiophene was carried out as a result of the in part simultaneous synthesis of the sulfur analogs of the indole alkaloids *ellipticine* and *olivacine* by Goodman, Campaigne, and Swan, and their co-workers.

Several important new synthetic routes to dibenzothiophenes have been described, including two routes to compounds substituted at C-1 and C-1,9, hitherto extremely inaccessible positions. The synthesis of several derivatives of (1) bearing substituents at C-9b or at S(5) has also been described, both novel types.

Probably the most important recent advance in the chemistry of dibenzothiophene has been the adoption of NMR techniques for structural determination. This will eliminate much of the tedious synthetic work which was previously needed to establish the structure of new derivatives.

II. Naturally Occurring Dibenzothiophenes

A. IN CRUDE OIL AND COAL TAR

Little information regarding the natural occurrence of dibenzothiophene was available for the period up to 1952.¹ Since then, the formidable task of separating and identifying sulfur compounds present in crude oil has represented part of the work of the Federal Bureau of Mines in cooperation with the American Petroleum Institute.^{2, 3}

As a result of this work reliable techniques⁴⁻⁹ for characterizing

² B. J. Mair, *Amer. Soc. Testing Mater., Spec. Tech. Publ.* **389**, 214 (1965); *Chem. Abstr.* **64**, 15640 (1966).

³ C. J. Thompson, H. J. Coleman, R. L. Hopkins, and H. T. Rall, *Amer. Soc. Testing Mater., Spec. Tech. Publ.* **389**, 329 (1965); *Chem. Abstr.* **64**, 15640 (1966).

⁴ H. J. Coleman, N. G. Adams, B. H. Eccleston, R. L. Hopkins, L. Mikkelsen, H. T. Rall, D. Richardson, C. J. Thompson, and H. M. Smith, *Anal. Chem.* **28**, 1380 (1956).

⁵ H. J. Coleman, C. J. Thompson, C. C. Ward, and H. T. Rall, *Anal. Chem.* **30**, 1592 (1958).

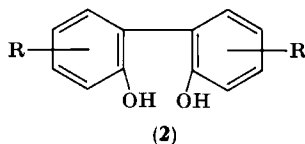
⁶ H. J. Coleman, C. J. Thompson, H. T. Rall, and H. M. Smith, *Anal. Chem.* **27**, 175 (1955).

⁷ H. J. Coleman, C. J. Thompson, H. T. Rall, and R. L. Hopkins, *Proc. Amer. Petrol. Inst.* **42**, Sect. 8, 46 (1962).

⁸ H. E. Lumpkin and B. H. Johnson, *Anal. Chem.* **26**, 1719 (1954).

⁹ H. V. Drushel and J. F. Miller, *Anal. Chem.* **30**, 1271 (1958).

small quantities of material have been established. Analysis of four crude oils has indicated the presence of approximately 200 individual sulfur compounds split into 13 main classes, one of which represents dibenzothiophene and its derivatives. For example, both dibenzothiophene and tetrahydrodibenzothiophene derivatives are thought to be present in a high-boiling (225°–400°) Wasson, Texas, crude oil distillate.¹⁰ Both 4-methyl- and 4,6-dimethyldibenzothiophenes are included in the 21 compounds which have been isolated^{2, 11, 12} from the trinuclear aromatic portion of a heavy gas oil and light lubricating distillate. Distillation of the heavy fractions of Lacq petroleum has yielded 23 fractions¹³ from which dibenzothiophene itself, together with 4-methyldibenzothiophene and 3 other derivatives, possibly 2-methyl-, 4,6-dimethyl-, and a trimethyldibenzothiophene, have been isolated, although some confusion over the melting point of the 4-methyl derivative has arisen^{2, 11–13} (Section VI,A,1). Kuwait distillates, which are known to have an unusually high sulfur content, contain considerable amounts of alkylidibenzothiophenes, including 4,6-dimethyldibenzothiophene and 2,3,6,7-, 2,3,6,8-, 2,4,6,8-, and 3,4,6,7-tetramethyldibenzothiophene.^{14–17} It is believed¹⁷ that possible precursors of dibenzothiophenes in oil may be dihydroxybiphenyl derivatives of type (2) formed from ortho-coupling of phenols which are known to be present in crude oils.¹⁸ Dibenzothiophene derivatives have also been shown to be present in both light¹⁹ and heavy²⁰ catalytic cycle oils and Middle East lubricating oils²¹



¹⁰ C. J. Thompson, N. G. Foster, H. J. Coleman, and H. T. Rall, *U.S. Bur. Mines, Rep. Invest.* **6879** (1966); *Chem. Abstr.* **66**, 47985 (1967).

¹¹ B. J. Mair and J. L. Martín-Picó, *Proc. Amer. Petrol. Inst.* **42**, Sect. 3, 173 (1962).

¹² B. J. Mair, *Chem. Eng. News*, **40** (10), 54 (1962).

¹³ L. Espagno and B. Poquet, *J. Chim. Phys.* **59**, 509 (1962).

¹⁴ W. Carruthers, *Nature (London)* **176**, 790 (1955).

¹⁵ W. Carruthers and A. G. Douglas, *J. Chem. Soc.*, 2813, (1959).

¹⁶ W. Carruthers and A. G. Douglas, *J. Chem. Soc.*, 278 (1957).

¹⁷ W. Carruthers and A. G. Douglas, *J. Chem. Soc.*, 4077 (1964).

¹⁸ H. L. Lochte and E. R. Littmann, "The Petroleum Acids and Bases," Chapter 12. Constable, London, 1955.

¹⁹ T. Acel, K. W. Bartz, H. E. Lumpkin, and F. C. Stehling, *Anal. Chem.* **34**, 1821 (1962).

²⁰ D. P. Montgomery, *J. Chem. Eng. Data* **8**, 432 (1963).

²¹ E. Kado and K. Kado, *Yukagaku* **6**, 273 (1957); *Chem. Abstr.* **55**, 4937 (1961).

and dibenzothiophene and alkyl derivatives including 4,6-dimethyl-dibenzothiophene have been detected in anthracene oil.^{22, 23} Technical phenanthrene obtained from coal tar is known²⁴⁻²⁶ to be contaminated with up to 6-8% dibenzothiophene as well as with the more readily detected anthracene. Although large-ring sulfur compounds are believed²⁷⁻²⁹ to be present in coal, these, under pyrolysis, may well break down to give dibenzothiophene and this compound has in fact been detected in oil and coal-tar pitch formed from the low-temperature carbonization of coal in layered beds²⁸⁻³¹ and from the high-temperature carbonization of bituminous coal.³² It has also been detected in creosote-impregnated wood.³³

B. SEPARATION TECHNIQUES

Separation of dibenzothiophene derivatives from petroleum oil fractions has been achieved by integrated approaches^{2, 11, 12} in which fractionating processes^{10, 13, 15} such as isothermal distillation, vacuum fractionation, and molecular distillation have been combined with spectroscopic methods including mass spectrometry^{2, 3, 10-13, 34, 35} and NMR spectroscopy.^{2, 11} Dibenzothiophenes have also been concentrated in sharp chromatographic fractions obtained, for example, by alumina gel percolation,¹⁹ and have been detected by gas chromatography.^{3, 20, 22, 31-33, 36} Gas chromatography has also been used to

²² E. Proksch, *Oesterr. Chem.-Ztg.* **67**, 105 (1966); *Chem. Abstr.* **64**, 19251 (1966).

²³ O. Kruber and A. Raeithel, *Chem. Ber.* **87**, 1469 (1954).

²⁴ L. D. Gluzman and V. M. Efimenko, *Sb. Nauch. Tr. Ukr. Nauch.-Issled. Uglek-him. Inst.* **16**, 151 (1965); *Chem. Abstr.* **64**, 3253 (1966).

²⁵ E. A. Johnson, *J. Chem. Soc.*, 948 (1962).

²⁶ O. Kruber, German Patent 832,152 (1952); *Chem. Abstr.* **52**, 9572 (1958).

²⁷ G. K. Angelova and K. I. Syskov, *Izv. Akad. Nauk SSSR, Otd. Tekh. Nauk. Met. Topl.* **5**, 153 (1959); *Chem. Abstr.* **55**, 16960 (1961).

²⁸ H. W. Sternberg, C. L. Delle Donne, R. E. Markby, and I. Wender, *Fuel* **45**, 469 (1966).

²⁹ H. W. Sternberg, C. L. Delle Donne, and I. Wender, *Fuel* **47**, 219 (1968).

³⁰ H. G. Franck, *Brennst.-Chem.* **33**, 37 (1953).

³¹ J. Andre, D. Dath, J. Mahieu, and E. H. Grand'Ry, *Brennst.-Chem.* **48**, 369 (1967).

³² J. L. Schultz, R. A. Friedel, and A. G. Sharkey, Jr., *Fuel* **44**, 55 (1965).

³³ H. J. Petrowitz and G. Becker, *Materialpruefung* **6**, 461 (1964); *Chem. Abstr.* **62**, 12385 (1965).

³⁴ S. H. Hastings, B. H. Johnson, and H. E. Lumpkin, *Anal. Chem.* **28**, 1243 (1956).

³⁵ S. Oshima, K. Fujii, and M. Nakai, *Shitsuryo Bunseki* **14**, 209 (1966); *Chem. Abstr.* **69**, 60461 (1968).

³⁶ A. Giraud and M. A. Bestougeff, *J. Gas Chromatog.* **5**, 464 (1967).

separate mixtures of sulfones³⁷ including that of dibenzothiophene. Mixtures of dibenzothiophene and either phenanthrene or dibenzofuran have been successfully separated³⁸ by TLC using petroleum ether and alumina-impregnated glass paper. Paper and TLC chromatography have also been used^{39, 40} to separate complex mixtures, detection of bands being accomplished either by fluorescence and phosphorescence colors⁴⁰⁻⁴⁵ or by color tests.⁴⁶⁻⁵³ Mixtures of homologous mercaptans, sulfides, sulfoxides, and dibenzothiophene derivatives have also been separated by adsorption and distribution TLC using a combined double-dimensional procedure.⁵⁴ Separation of mixtures of heterocycles including dibenzothiophene, its sulfoxide and sulfone has been achieved using either⁵⁵ silica gel or alumina in hexane or carbon tetrachloride, and the use of silica^{34, 35} alone in, for example, isooctane has been studied.⁵⁶ Lipophilic organic polymers of the "Porapak" type have also been used.⁴⁸ The poisoning of platinum, palladium, nickel, and other metallic catalysts by sulfur compounds and the Raney nickel desulfurization of these compounds is known^{57, 58} to involve initial chemisorption onto the

³⁷ V. E. Cates and C. E. Meloan, *J. Chromatog.* **11**, 472 (1963).

³⁸ L. H. Klemm, E. P. Antoniadis, G. Capp, E. Chiang, and E. Y. K. Mak, *J. Chromatog.* **6**, 420 (1961).

³⁹ M. Sterescu and N. Keim, *Rev. Chim. (Bucharest)* **10**, 712 (1959).

⁴⁰ E. Sawicki, H. Johnson, and K. Kosinski, *Microchem. J.* **10**, 72 (1966).

⁴¹ M. Sterescu, N. Keim, and M. Popa, *Rev. Chim. (Bucharest)* **11**, 487 (1960).

⁴² A. Szent-Györgyi, *Science* **126**, 751 (1957).

⁴³ M. Zander, *Erdoel Kohle* **15**, 362 (1962).

⁴⁴ E. Sawicki and H. Johnson, *Microchem. J.* **8**, 85 (1964).

⁴⁵ H. V. Drushel and A. L. Sommers, *Anal. Chem.* **98**, 10 (1966).

⁴⁶ C. Karr, *Anal. Chem.* **26**, 528 (1954).

⁴⁷ N. Kucharazyk, J. Fohl, and J. Vymetal, *J. Chromatog.* **11**, 55 (1963).

⁴⁸ J. Janak and V. Kubecova, *J. Chromatog.* **33**, 132 (1968).

⁴⁹ V. E. Levine and M. Nachman, *J. Forensic Med.* **10**, 65 (1963).

⁵⁰ P. Jacquignon, N. P. Buu-Hoi, and M. Mangane, *Bull. Soc. Chim. Fr.*, 2517 (1964).

⁵¹ E. Sawicki, *Chem. Anal.* **46**, 67 (1957).

⁵² H. D. Hartough, *Anal. Chem.* **23**, 1128 (1951).

⁵³ E. Sawicki, T. W. Stanley, and T. R. Hauser, *Chem. Anal.* **47**, 69, 77 (1958).

⁵⁴ H. W. Prinzler, D. Pape, H. Tauchmann, M. Teppke, and C. Tzscharnke, *Ropa Uhlie* **8**, 13 (1966); *Chem. Abstr.* **65**, 9710 (1966).

⁵⁵ D. Pape, M. Teppke, and H. W. Prinzler, *Conf. Chem. Process Petrol. Natur Gas, Plenary Lect.*, 1965, 579 (1968), *Chem. Abstr.* **70**, 53766 (1969).

⁵⁶ G. D. Galpern, E. N. Karaulova, and T. S. Novazhilova, *Tr. Inst. Nefti, Akad. Nauk. SSSR* **13**, 51 (1959); *Chem. Abstr.* **55**, 6989 (1961).

⁵⁷ B. Juguin, C. Clement, P. Leprince, and R. Montarnal, *Bull. Soc. Chim. Fr.* 709 (1966).

⁵⁸ E. B. Maxted, *Advan. Catal.* **3**, 129 (1951).

catalyst via the lone pair of electrons of the sulfur atom. This fact has been used to advantage in the separation of mixtures of dibenzothiophene and biphenyl, a column of Raney cobalt and sand being particularly useful.⁵⁹ A method of preferential extraction of dibenzothiophene-type compounds from lubricating oils using mercuric acetate has been developed²¹ and extended to liquid-liquid chromatographic systems⁶⁰ employing a stationary phase of mercuric acetate in acetic acid with *n*-hexane as the mobile phase. Such systems are useful for separation of alkyl and cycloalkyl sulfides from most of the other classes of organic compounds found in petroleum, both simple and condensed thiophenes such as dibenzothiophene being readily eluted. Complex mixtures of polycyclic aromatic hydrocarbons including dibenzothiophene have also been separated nondestructively using a solvent system incorporating tetramethyluric acid⁶¹ as a selective complexing agent or by forming solid addition compounds with cold hexafluorophosphoric acid⁶² or by adding thiourea, compounds other than dibenzothiophene forming weaker adducts.^{20, 63} Although dibenzothiophene may be separated²⁶ from technical phenanthrene²⁵ by crystallization from benzene, destructive methods of removal have been reported involving oxidation with peracetic acid at 100° to give the sulfone together with a biphenyl carboxylic acid which is readily soluble in aqueous alkali.^{24, 35} A more drastic method of removal of dibenzothiophene from oil involves oxidation and treatment of the sulfone thus formed with an alkali metal hydroxide to give the corresponding dibenzofuran derivative (see Section III, C, 2).⁶⁴

III. Molecular Structure and Physical Properties of Dibenzothiophenes

A. MOLECULAR ORBITAL TREATMENTS OF DIBENZOTHIOPHENE

Several molecular orbital treatments of dibenzothiophene have appeared, the object in general being twofold. First, to derive a model which will account for the positional electrophilic reactivity observed for dibenzothiophene, and second, as a result of such a model, to formulate an accurate quantum mechanical model for the sulfur atom and empirical

⁵⁹ G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chromatog.* **13**, 234 (1964).

⁶⁰ W. L. Orr, *Anal. Chem.* **38**, 1558 (1966).

⁶¹ J. D. Mold, T. B. Walker, and L. G. Veasey, *Anal. Chem.* **35**, 2071 (1963).

⁶² N. V. de Bataafsche Petroleum Maatschappij, British Patent 723,185 (1955); *Chem. Abstr.* **49**, 9918 (1955).

⁶³ D. P. Montgomery, U.S. Patent 3,257,376 (1966); *Chem. Abstr.* **65**, 8848 (1966).

⁶⁴ Esso Research and Eng. Co., Neth. Application 6,602,260 (1966), *Chem. Abstr.* **66**, 4760 (1967).

parameters for both the sulfur atom and the C-S bond in condensed thiophenic heterocycles. Only moderate success has been achieved in predicting reactivities although the prediction of electronic spectra using these methods has been more rewarding. The problem in general is associated with the selection of suitable parameters for the sulfur atom, those required for the carbon atoms being well established.⁶⁵

As with the related treatments of the π -electron system of benzo[b]-thiophene⁶⁶ and other sulfur-containing heterocycles,^{67, 68} two different models have been employed for dibenzothiophene. The first^{67, 69} (Model A) assumes participation of the sulfur 3d orbitals in the form of $3pd^2$ hybrids⁷⁰ and thus makes the sulfur atom analogous to the $-\text{CH}=\text{CH}-$ group in alternant hydrocarbons. The second^{67, 69, 71} (Model B) regards the sulfur atom as a replacement for the $-\text{CH}_2-$ group in fluorene. Model A predicts approximately the same reactivity to electrophilic substitution for positions 2, 3, and 4. On the other hand, Model B predicts that position 3 will be less active than positions 2 and 4, and with the correct choice of parameters position 2 can be made the most active with this model.⁶⁷ The use of the Kikuchi thiophene parameters (in particular adoption of the modified C-S Coulomb integral which gives the sulfur orbitals electropositive character) in dibenzothiophene gives π -electron densities in closest agreement with observed reactivity, i.e., $2 > 4 > 3 \gg 1$.⁷² Despite this agreement it is now considered⁷³⁻⁷⁷ that the "d" orbitals of the sulfur atom play a negligible part in the ground state and first excited states of dibenzothiophene and related heterocycles. In particular, the charge on the sulfur atom in dibenzothiophene has been estimated from the frequency of the K_α doublet in its X-ray spectrum

⁶⁵ N. Trinajstić and A. Hinchliffe, *Z. Phys. Chem. (Frankfurt)* [N.S.] **59**, 271 (1968).

⁶⁶ B. Iddon and R. M. Scrowston, *Advan. Heterocycl. Chem.* **11**, 365 (1970).

⁶⁷ R. Zahradník, C. Párkányi, V. Hořák, and J. Koutecký, *Collect. Czech. Chem. Commun.* **28**, 776 (1963).

⁶⁸ R. Zahradník, *Advan. Heterocycl. Chem.* **5**, 1 (1965).

⁶⁹ J. Koutecký, R. Zahradník, and J. Paldus, *J. Chim. Phys. Physicochim. Biol.* **56**, 455 (1959).

⁷⁰ H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

⁷¹ G. Berthier and B. Pullman, *Compt. Rend. Acad. Sci., Ser. C* **231**, 744 (1950).

⁷² K. Kikuchi, *Sci. Rep. Tohoku Univ., Ser. I* **41**, 35 (1957); *Chem. Abstr.* **52**, 14317 (1958).

⁷³ R. Zahradník, J. Fabian, A. Mehlhorn, and V. Kvasnicka, *Organosulfur Chem. Org. Sulfur Symp., 2nd, 1966*, 203 (1967); *Chem. Abstr.* **69**, 6368 (1968).

⁷⁴ F. P. Billingsley and J. E. Bloor, *Theor. Chim. Acta* **11**, 325 (1968).

⁷⁵ A. Mangini, *Pure Appl. Chem.* **7**, 103 (1963).

⁷⁶ R. Gerdil and E. A. C. Lucken, *J. Amer. Chem. Soc.* **87**, 213 (1965).

⁷⁷ R. Gerdil and E. A. C. Lucken, *J. Amer. Chem. Soc.* **88**, 733 (1966).

and found to be close to that of diphenyl sulfide.⁷⁵ In addition, comparison of the calculated hyperfine splitting constants in the ESR spectra of dibenzothiophene radical ions with the observed values has confirmed that the 3d orbitals can be neglected.⁷⁶

The Pariser–Parr–Pople semiempirical method has been applied to dibenzothiophene^{65, 73, 74, 78–80} to predict bond orders, relative electrophilic reactivities of the four positions, and to explain the electronic spectrum in terms of comparing theoretical excitation and transition energies with those obtained from near-ultraviolet and visible spectroscopy. Although this approach was able to predict fairly accurately the energy of the first π – π^* transition⁶⁵ (5.51 eV observed, 5.30 eV calculated) it was unable to explain the fact that most of the electrophilic reactions of dibenzothiophene occur in the 2-position. It, in fact, predicted the order $4 > 2 > 3 > 1$ for electrophilic attack and positions 3 and 7 for nucleophilic attack.⁶⁵ Perhaps partial confirmation of the latter prediction was afforded recently by the reaction of methoxide ion with octafluorodibenzothiophene, which gave the 3-methoxy and 3,7-dimethoxy derivatives.⁸¹

Spin-density distributions for the radical anions of several compounds including dibenzothiophene have been calculated using the unrestricted Hartree–Fock method. Calculated values were of the same order as observed values but close agreement was not obtained.⁸² Hyperfine splitting constants were also calculated using both Model A and Model B as defined earlier; results favored Model B.⁷⁶

B. SPECTROSCOPY

1. NMR Spectra

The 60 MHz NMR spectrum of dibenzothiophene has been measured in chloroform- d_1 ,² carbon tetrachloride,^{83, 84} and acetone.^{83, 84} The 100 MHz spectrum, which is shown in Fig. 1, has been measured in

⁷⁸ F. Dorr and G. Hohlneisher, *Proc. Eur. Congr. Mol. Spectrosc.*, 8th, 1965.

⁷⁹ J. Fabian, A. Mehlhorn, and R. Zahradník, *J. Phys. Chem.* **72**, 3975 (1968).

⁸⁰ J. Fabian, A. Mehlhorn, and R. Zahradník, *Theor. Chim. Acta* **12**, 247 (1968).

⁸¹ R. D. Chambers and D. J. Spring, *Tetrahedron* **27**, 669 (1971).

⁸² N. K. Ray and P. T. Narasimhan, *Theor. Chim. Acta* **11**, 156 (1968).

⁸³ P. Faller, *Bull. Soc. Chim. Fr.*, 387 (1967).

⁸⁴ K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron* **27**, 5177 (1971).

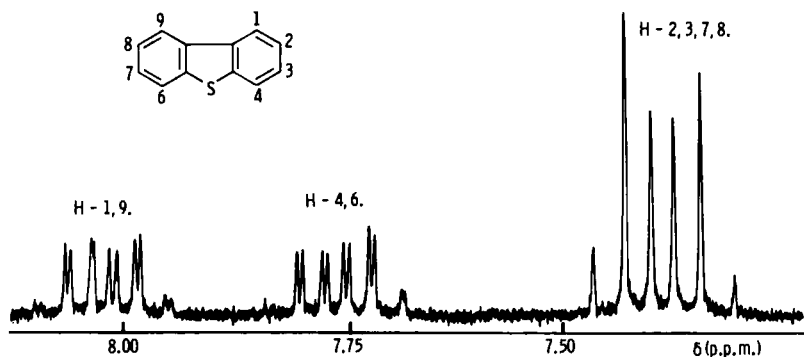


FIG. 1. NMR spectrum at 100 MHz of dibenzothiophene (CDCl_3). Adapted from Balkau *et al.*

chloroform- d_1 ,^{85, 86} carbon tetrachloride,⁸⁴ acetone,^{84, 86, 87} benzene- d_6 ,⁸⁶ and in the molten state at 100° .⁸⁶ The first NMR spectrum of dibenzothiophene was recorded in 1965, by Mair, who assigned the low-field multiplet at ~ 8.0 to H-1,9, the multiplet at ~ 7.75 to H-4,6 and the high-field multiplet to H-2,3,7, and 8.² These assignments, which were used by Mair to establish the structure of 4,6-dimethyldibenzothiophene, were based on the estimated effect of ring currents on the four proton environments and have been used since with growing confidence, culminating in a definite proof of assignment by Balkau and Heffernan in 1971.⁸⁸ Having stated this, it is worth noting that at the time of Mair's work 4,6-dimethyldibenzothiophene was already a known compound,²³ thus the absence of a multiplet at ~ 7.75 in its spectrum could have been used to associate this multiplet in the spectrum of dibenzothiophene with H-4,6. Nevertheless, up until very recently the question of assignment of the low-field multiplet to H-4,6 or H-1,9 was still being debated. The existence of such well-separated multiplets is proving to be of great value in establishing the structure of derivatives of dibenzothiophene. The spectra of a large number of mono- and disubstituted derivatives, both homo- and heteronuclear, have been recorded^{2, 85, 89-92} and in all cases the protons of the unsubstituted ring

⁸⁵ E. Campaigne and J. Ashby, *J. Heterocycl. Chem.* **6**, 517 (1969).

⁸⁶ F. Balkau, M. W. Fuller, and M. L. Heffernan, *Aust. J. Chem.* **24**, 2293 (1971).

⁸⁷ B. Clin and B. Lemancheau, *J. Chim. Phys. Physicochim. Biol.* **66**, 1327 (1969).

⁸⁸ F. Balkau and M. L. Heffernan, *Aust. J. Chem.* **24**, 2305 (1971).

⁸⁹ E. Campaigne, J. Ashby, and L. Hewitt, *J. Heterocycl. Chem.* **6**, 553 (1969).

⁹⁰ E. Campaigne, L. Hewitt, and J. Ashby, *J. Heterocycl. Chem.* **6**, 753 (1969).

⁹¹ A. N. Fujiwara, E. M. Acton, and L. Goodman, *J. Heterocycl. Chem.* **5**, 853 (1968).

⁹² B. C. Elmes and J. M. Swan, *Aust. J. Chem.* **22**, 1963 (1969).

give a spectrum essentially the same as the total spectrum (Fig. 1). Superimposed upon this spectrum are the resonances of the remaining protons of the substituted ring, the chemical shifts and coupling constants of which invariably indicate the structure of the compound unequivocally.

The structures of a series of homonuclear substitution products of 4-methyl-⁸⁹ and 4-methoxydibenzothiophene⁹⁰ have been determined by the above methods. In the case of bromination products the structures were established by conversion to the corresponding aldehydes the spectra of which exhibited the expected large deshielding effect on ortho protons. Assignments were further confirmed by reduction of the aldehydes to the methyl compounds, which had the effect of reversing the aldehyde shifts. Of particular interest in this series was the spectrum of 4-methoxy-1-dibenzothiophenecarboxaldehyde⁹⁰ in which the resonance of H-9 occurred at $\delta 9.12$, being deshielded by the 1-CHO group, probably by a through space effect. This observation coupled with n.O.e. experiments conducted on 1,4-dimethyldibenzothiophene⁹² and the detection of interring coupling between H-1 and H-9⁸⁸ serve to remove any doubts about the accepted spectral assignments for dibenzothiophene.

The deshielding of H-1,9 and to a lesser extent H-4,6 has been attributed to their proximity to the thiophene ring and in the case of H-1 and 9 proximity to the second anisotropic six-membered ring.^{88, 93} This "ring current" explanation is favored^{88, 93} over the assumption that H-1 and 9 are in Van de Waals contact, thereby causing deshielding. Methyl substituents at C-1 or 9 are similarly deshielded, for example, the methyl resonances of 2-, 3-, and 4-methyldibenzothiophene occur between $\delta 2.42$ and 2.48 ^{85, 89} while the spectrum of 1,4-dimethyldibenzothiophene shows a singlet at $\delta 2.48$ associated with the 4-CH₃ group and a deshielded singlet at $\delta 2.78$ associated with the 1-CH₃ group.^{91, 92} Similarly the methyl resonance in 1-methyldibenzothiophene occurs at $\delta 2.82$.⁹⁴ The methyl resonance in 4,6-dimethyldibenzothiophene occurs at $\delta 2.6$, but the solvent was not specified.² The 60 MHz NMR spectrum of 1,3,7,9-tetramethyldibenzothiophene has been recorded⁹⁵; however, based on the above considerations the resonance at $\delta 2.7$ is undoubtedly associated with the C-1,9 methyl groups and that at $\delta 2.4$ with the C-3,7 methyl groups. The reverse assignment was made. Furthermore

⁹³ A. R. Frasca, *An. Ass. Quim. Argent.* **56**, 149 (1968); *Chem. Abstr.* **74**, 63625 (1971).

⁹⁴ J. Ashby, unpublished results (1972).

⁹⁵ P. Canonne and J. Gourier, *Compt. Rend. Acad. Sci., Ser. C* **268**, 2319 (1969).

there is no explanation of the fact that the resonances of H-2,8 and H-4,6 occur at $\delta 6.66$ and 6.96 , respectively. Comparison with related spectra^{85, 89, 91} would indicate that $\delta 7.1$ and 7.5 would be more realistic chemical shifts for these protons.

A small overall deshielding (~ 0.1 ppm) of protons in the unsubstituted ring has been observed for derivatives bearing an electron-withdrawing substituent at either C-1⁹⁰ or C-3.⁸⁵

The spin-spin coupling constants for the spectrum of dibenzothiophene in carbon tetrachloride and acetone have been accurately determined by computer analysis and listed.⁸⁴ In routine structural studies of derivatives of dibenzothiophene it is usually found that ortho-couplings are close to 8 Hz, meta couplings about 2 Hz and $J_{1,4}$ between 0.5 and 1 Hz. In chloroform- d_1 , H-2 and 3 in dibenzothiophene have the same chemical shift⁸⁶ and the spectrum of 1,4-dimethyldibenzothiophene in this solvent also shows H-2,3 as a singlet at $\delta 7.03$.⁹¹ Apart from the minimal coupling which has been detected⁸⁸ between H-1,9 of ~ 0.08 Hz, no interring coupling is observed in dibenzothiophenes.

Several attempts to analyze the spectrum of dibenzothiophene have been made. The first, by Faller,⁸³ treated the spectrum as an approximate ABMX system using the direct method of Batterham. This gave a calculated spectrum in reasonable agreement with the deceptively simple chloroform- d_1 spectrum, where in $\delta 2 = \delta 3$. A similar analysis of the spectrum of both dibenzothiophene and 5-methyldibenzothiophenium perchlorate has recently been made at 60 and 100 MHz.⁹⁶ The spectrum of dibenzothiophene in acetone or carbon tetrachloride has more resolved lines in it due to the nonequivalence of the chemical shifts of H-2,3 in these solvents. Such a situation is suitable for more refined computations of the spectrum. Three iterative analyses of the 100 MHz spectrum in acetone have been made starting with ABMX parameters,^{84, 86, 87} and although the predicted spectrum fits well with the observed spectrum it is still somewhat insensitive to changes in some of the original parameters due to the similar shifts of H-2 and H-3. The best match between observed and calculated spectra was obtained by iterative analysis of the carbon tetrachloride or benzene- d_6 spectra as an ABCD system.^{84, 86} A prediction of such analyses is that $J_{1,2} > J_{3,4}$ and $J_{1,3} > J_{2,4}$ and this has been confirmed by a study of the ^{13}C -H satellite spectra of the benzene- d_6 spectrum.⁸⁶ "Spin-tickling" and other double irradiation experiments are consistent with all of the coupling constants in the spectrum of dibenzothiophene, being of the same sign.⁸⁶

The lines in the spectrum of dibenzothiophene are sensitive to changes

⁹⁶ R. M. Acheson and D. R. Harrison, *J. Chem. Soc. C*, 1764 (1970).

in solvent, acetone, for example, causing a marked deshielding. Such changes have been correlated with some measure of ordering of the polar solute molecules.^{84, 86} Comparisons of the aromaticity of dibenzothiophene with related compounds have been made based on chemical shifts and coupling constants.⁸⁴

A full iterative analysis of the more-complicated NMR spectra of both dibenzothiophene 5-oxide and 5,5-dioxide has been made. A slight broadening (~ 0.05 – 0.1 Hz) of the lines associated with one of the protons in both compounds was assumed to be due to $J_{1,9}$ and this was used to assign peaks in the spectra.⁸⁸

No significant pseudo-contact shifts could be induced in the spectra of dibenzothiophene, its sulfoxide, or its sulfone, with $\text{Eu}(\text{dpm})_3$ ⁸⁸ although a marked shielding of the protons of one ring was observed in the spectrum of the chromium tricarbonyl complex of dibenzothiophene,⁹⁷ presumably due to a contact shift mechanism.

2. Mass Spectra

Although the mass spectra of dibenzothiophene,^{98, 99} its sulfoxide,⁹⁹ and its sulfone^{100, 101} have been recorded, the bulk of published work in this area is mainly of a general nature concerned with the identification of types and classes of sulfur compounds. As a result, detailed fragmentation patterns of dibenzothiophene derivatives are few in number. Mass spectrometry, particularly low electron voltage mass spectrometry, has, however, been extensively used for the identification of dibenzothiophenes in petroleum.^{2, 3, 10–13, 19, 34, 35, 102}

If several similar compounds contain the same strongly directing functional group, differences in the identity and relative intensity of ions in their mass spectra can be correlated with molecular structure. The sulfur atom in dibenzothiophenes can be regarded as such a functional group, moreover, the CS fragment is known to be a stable leaving species and is readily eliminated from the molecular ion of dibenzothiophene under electron impact.^{98, 99} The ion thereby formed (3) can fragment in several ways: loss of a hydrogen radical giving m/e 139 (4),

⁹⁷ E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *Organomet. Chem.* **14**, 359 (1968).

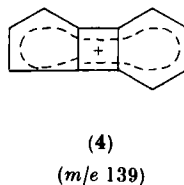
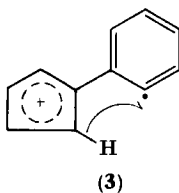
⁹⁸ J. H. D. Eland and C. J. Danby, *J. Chem. Soc.*, 5934 (1965).

⁹⁹ J. Heiss, K.-P. Zeller, and B. Zeeh, *Tetrahedron* **24**, 3255 (1968).

¹⁰⁰ E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.* **88**, 2836 (1966).

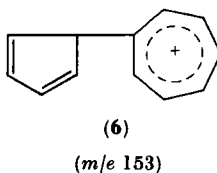
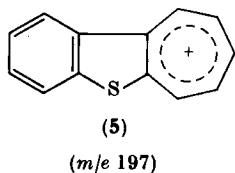
¹⁰¹ J. H. Bowie, D. H. Williams, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, and G. Schroll, *Tetrahedron* **22**, 3515 (1966).

¹⁰² A. Hood, in "Mass Spectrometry of Organic Ions" (F. W. McLafferty, ed.), p. 597. Academic Press, New York, 1963.



loss of acetylene giving *m/e* 114 which can lose a further hydrogen radical to give *m/e* 113, or loss of a methyl radical giving *m/e* 125.⁹⁸ Sulfur is also eliminated from the molecular ion, explaining the peak at *m/e* 152.⁹⁹ The formation of 4 has been studied¹⁰³ using dibenzothiophene specifically labeled at positions 4 and 6 with deuterium. Surprisingly, although the hydrogen atoms on C-4 and C-6 are closest to the sulfur atom in the original dibenzothiophene molecule, they are not preferentially lost during the formation of ion (4).¹⁰³ The four monotrityl derivatives of dibenzothiophene have been reported; however, their mass spectra were not recorded.¹⁰⁴ Unfortunately, a comprehensive study of the available spectra of dibenzothiophene and 17 similar compounds containing both thiophene and benzene rings showed no correlation between molecular structure and relative intensities of ions corresponding to primary loss of CS, CHS, acetylene, sulfur or hydrogen sulfide.¹⁰³ The spectra of dibenzothiophene and naphtho[2,3-*b*]thiophene are, for example, remarkably similar. Although the relative intensity of the ion at *m/e* 139 is greater in the spectrum of the naphthothiophene than in that of dibenzothiophene, the difference is only slight.¹⁰³

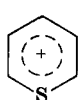
The spectrum of 1-methyldibenzothiophene⁹⁴ shows a strong ion at *m/e* 197, probably corresponding to formation of the tropylium ion (5) (80%). Ions at *m/e* 165, 164, and 153 are associated with losses of S, SH, and CS, respectively, from (5), the loss of CS giving the tropylium ion (6). Preferential fragmentation of ion (5) rather than the parent ion was supported by the appropriate metastable peaks.



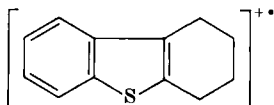
¹⁰³ S. Meyerson and E. K. Fields, *J. Org. Chem.* **33**, 847 (1968).

¹⁰⁴ R. Baker and C. Eaborn, *J. Chem. Soc.*, 5077 (1961).

A six-membered ring structure (7) has been suggested for the $C_5H_5S^+$ ion resulting from β -cleavage in alkylthiophenes.^{105, 106} Despite a general lack of reference spectra to support the applicability of this "ring expansion theory" to the thiophene ring of condensed thiophenes, it has been invoked in the case of ring-reduced dibenzothiophenes. Loss of ethylene from the molecular ion (8) of 1,2,3,4-tetrahydrodibenzothiophene could give the benzothiatropylium ion (9) and an ion at m/e 160 is reported for this compound at low ionizing voltage, indicating the low energy required for bond cleavage.¹⁰⁷⁻¹⁰⁹ However, the ion at m/e 160

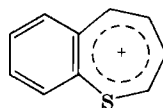


(7)



(8)

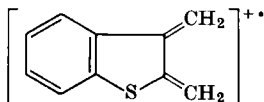
(m/e 188)



(9)

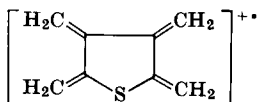
(m/e 160)

has also been formulated in the isomeric *exo*-methylene form (10),¹⁰⁷ and this would be more consistent with the fact that the spectrum of octahydrodibenzothiophene shows an ion at m/e 164 (100%) corresponding to a similar retro-Diels-Alder loss of ethylene coupled with an ion at m/e 136 (19%) due to a further loss of ethylene.¹⁰⁹ The second loss of 28 mass units is consistent with the formation of 11 and argues against intermediate formation of a thiatropylium ion, as originally proposed.¹⁰⁹ The thiapyrylium ion (12) has been suggested to account



(10)

(m/e 160)



(11)

(m/e 136)

for the ion at m/e 198 observed in the mass spectra of some *S*-alkyldibenzothiophenium salts.⁹⁶

¹⁰⁵ V. Hanuš and V. Čermák, *Collect. Czech. Chem. Commun.* **24**, 1602 (1959).

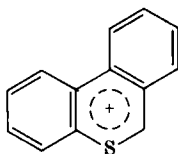
¹⁰⁶ H. M. Grubb and S. Meyerson, in "Mass Spectrometry of Organic Ions" (F. W. McLafferty, ed.), p. 453. Academic Press, New York, 1963.

¹⁰⁷ H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," p. 632. Holden-Day, San Francisco, 1967.

¹⁰⁸ "Catalog of Mass Spectral Data," Amer. Petrol. Inst. Res. Project No. 44. Carnegie Inst. Technol., Pittsburgh, Pennsylvania.

¹⁰⁹ G. L. Cook and N. G. Foster, *Proc. Amer. Petrol. Inst.* **41**, Sect. 3, 199 (1961).

The pyrolysis of dibenzothiophene 5,5-dioxide has been shown to occur via the ring-expanded sulfinic ester, which eliminates SO to give the strainless dibenzofuran (see Section III, C, 1). An expected product of

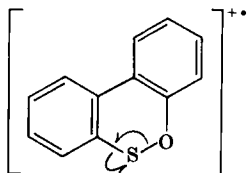


(12)

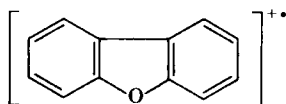
(m/e 198)

pyrolysis, biphenylene, was not detected.¹⁰⁰ This parallels its behavior under electron impact, major primary decomposition processes involving not only elimination of SO but also successive loss of carbon monoxide from the molecular ion.^{100, 101} A similar consistency was observed for octafluorodibenzothiophene 5,5-dioxide where an abundant peak at m/e 312, corresponding to $M^+ - SO$, was detected.^{110, 111} In contrast γ -radiolysis of dibenzothiophene sulfone with a cobalt-60 source at a dose rate of 0.7 Mrad/hr has, however, shown elimination of sulfur dioxide to occur, the loss being linear with dose to 13 Mrad, after which it levelled off. Again, no biphenylene was detected.¹¹²

The fragmentation of dibenzothiophene sulfoxide resembles that of dibenzothiophene rather than that of the sulfone. This is due to primary loss of O to give the dibenzothiophene ion, which is the strongest feature of the spectrum. Much of the breakdown which follows is due to that of the dibenzothiophene ion. There are, however, some aspects of sulfone behavior, notably the formation of the dibenzofuran ion (14) by the loss of sulfur from the rearranged molecular ion (13).⁹⁹



(13)



(14)

¹¹⁰ R. D. Chambers, J. A. Cunningham, and D. J. Spring, *J. Chem. Soc. C*, 1560 (1968).

¹¹¹ N. Kharasch and Z. S. Ariyan, *Chem. Ind. (London)*, 302 (1965).

¹¹² L. Kevan, P. L. Hall, and E. T. Kaiser, *J. Phys. Chem.* **70**, 853 (1966).

The occurrence of fragment ions arising by skeletal-rearrangement processes during the breakdown of sulfur compounds, in general, gives rise to rearrangement peaks which are considered to limit the use of positive-ion mass spectra for structure elucidation.¹¹³ The negative-ion spectra of aromatic sulfur compounds, however, differ markedly from the corresponding positive-ion spectra in that fragmentation patterns are simple, there being no ions which may be attributed to skeletal-rearrangement species. Species which in positive-ion spectra may give rise to stable cations such as tropylium ions are lost as radicals from the molecular anions with the other fragment retaining the negative charge. Accordingly, the negative-ion spectrum of dibenzothiophene 5,5-dioxide has been recorded and shows a single pronounced peak due to the molecular anion.¹¹³

3. IR Spectra

Much of the present knowledge regarding band assignments in the IR spectrum of dibenzothiophene¹¹⁴⁻¹¹⁶ and its derivatives has been gained in order to distinguish between various condensed thiophenes present in petroleum fractions or pyrolysis products. Dibenzothiophene gives^{117, 118} absorption bands at 2960 (w), 3017 (m), 3049 (s), and 3111 (w) cm^{-1} in the CH stretching^{119, 120} region. The main band at 3049 cm^{-1} is typical of tricyclic compounds such as anthracene, phenanthrene, and thianthrene, all of which give a main band in the 3047–3053 cm^{-1} region regardless of whether sulfur is present or not.¹¹⁷ The CH out-of-plane bending frequencies¹²⁰ for the two benzene rings occur at 862 (w), 768 (w), 745 (s), 732 (s), 728 (m), and 702 (m), the two strong bands indicating the presence of four adjacent hydrogen atoms.¹¹⁷

Bands arising in the spectra of condensed thiophenes¹²¹ in the region 2000–1666 cm^{-1} arise from overtone or combination vibrations¹²² due

¹¹³ J. H. Bowie, S.-O. Lawesson, J. Ø. Madsen, and C. Nolde, *Ark. Kemi* **31**, 481 (1969).

¹¹⁴ "Sadtler Standard Spectra." Sadtler Res. Lab. Inc., Philadelphia, Pennsylvania.

¹¹⁵ "Catalog of Infrared Spectral Data." Thermodynamics Res. Center, Texas A of M University, College Station, Texas (in collaboration with the Amer. Petrol. Inst.).

¹¹⁶ O. R. Sammul, W. L. Brannon, and A. L. Hayden, *J. Ass. Offic. Agr. Chem.* **47**, 918 (1964).

¹¹⁷ S. E. Wiberley and R. D. Gonzalez, *Appl. Spectrosc.* **15**, 174 (1961).

¹¹⁸ R. Joeckle, E. Lemperle, and R. Mecke, *Z. Naturforsch. A* **22**, 403 (1967).

¹¹⁹ C. G. Cannon and G. B. B. Sutherland, *Spectrochim. Acta* **4**, 373 (1951).

¹²⁰ L. J. Bellamy, "The Infrared Spectra of Complex Molecules," p. 64. Wiley, New York, 1958.

to out-of-plane deformation fundamentals of the hydrogens on the benzene ring. It has been suggested that the spectral pattern displayed by substituted benzenes in this region depends only on the number and location of substituents in the aromatic system.¹²² Accordingly, 1,2,3,4-tetrahydrodibenzothiophene shows a complex absorption pattern in this region characteristic of four adjacent hydrogens.¹²¹ Similar characteristics are shown by 3-methyldibenzothiophene but the pattern is further complicated in this case by the presence of one isolated and two adjacent hydrogens. The in-plane deformation region^{120, 120a} (1250–909 cm^{-1}) has been assigned¹²¹ for 1,2,3,4-tetrahydrodibenzothiophene and its 7-methyl derivative, as has the out-of-plane CH deformation region^{120, 123, 123a} (1000–667 cm^{-1}) for these two compounds and 3-methyldibenzothiophene. 4-Vinyldibenzothiophene gives a characteristic band at 745 cm^{-1} due to ortho substitution to a ring sulfur atom,¹²⁴ but supporting data for other 4-substituted dibenzothiophenes are lacking.

The asym and sym frequencies of the O=S=O stretching vibrations in dibenzothiophene 5,5-dioxide and its 2- and 3-nitro derivatives have been determined.¹²⁵ The sulfone shows a single band at 1309 cm^{-1} (asym O=S=O) and bands at 1161 and 1171 cm^{-1} (sym O=S=O),¹²⁶ the relative intensities of the bands varying with the nature and positions of substituent groups. A linear dependence of the ratio of the molar extinction coefficients of the asym and sym stretching vibrations of the nitro group on the reactivity of the position to which it is attached has been found for a group of polynuclear aromatic nitro compounds.¹²⁷ This work has now been extended to a study of sulfones, including dibenzothiophene 5,5-dioxide, and has shown that the ratio of the true absorption intensities of the asym and sym O=S=O stretching vibrations increases with increasing mesomeric interaction of the sulfone group with the rest of the molecule. The use of this ratio in the characterization of sulfones has been discussed.¹²⁶ Such characterization is not available for sulfoxides, but the IR spectrum of dibenzothiophene 5-

^{120a} D. H. Whiffen, *Spectrochim. Acta* **7**, 253 (1955).

¹²¹ F. R. McDonald and G. L. Cook, *U.S. Bur. Mines, Rep. Invest.* **6911** (1967); *Chem. Abstr.* **67**, 58846 (1967).

¹²² C. W. Young, R. B. DuVall, and N. Wright, *Anal. Chem.* **23**, 709 (1951).

¹²³ D. Cagniant, P. Faller, and P. Cagniant, *Bull. Soc. Chim. Fr.*, 2410 (1961).

^{123a} D. Cagniant, P. Cagniant, and J. Trierweiler, *Bull. Soc. Chim. Fr.*, 601, 607 (1969).

¹²⁴ W. A. Hewett and E. Gipstein, *Polym. Lett.* **6**, 565 (1968).

¹²⁵ N. Marziano and G. Montaudo, *Gazz. Chim. Ital.* **91**, 587 (1961).

¹²⁶ R. Zahradník and K. Bocek, *Spectrochim. Acta* **18**, 564 (1962).

¹²⁷ R. Zahradník and K. Bocek, *Collect. Czech. Chem. Commun.* **26**, 1733 (1961).

oxide has been recorded to confirm the identity of a reaction product.¹²⁸ IR spectroscopy has been used to study the equilibrium constant and hydrogen-bond shifts of a phenol-dibenzothiophene π -complex.¹²⁹

4. UV and Charge-Transfer Spectra

The interpretation and correlation of the electronic absorption and emission spectra of dibenzothiophene and its derivatives has been mainly qualitative, although several quantitative treatments have been described.^{65, 67, 73, 79, 80, 130} The UV absorption pattern of thiophene, unlike that of pyrrole or furan, resembles that of benzene.¹³¹ This behavior has been associated with the similar electronegativity of the sulfur and carbon atoms which facilitates participation of the sulfur lone-pair electrons with the aromatic system.¹³² Moreover, it has been suggested that these electrons occupy $3p d^2$ orbitals, thereby enhancing conjugation with the carbon π -electrons.¹³³ Such arguments have been forwarded to explain the similarity of the spectra of dibenzothiophene and phenanthrene.¹³⁴ Reservations on the validity of d-orbital participation in thiophenic systems are discussed in Section III,A. Spectral comparisons have also been made with other structurally related compounds such as dibenzoselenophene^{77, 135} and dibenzofuran.^{77, 130, 130a, 136-140} The spectral features of dibenzothiophene are very similar to those of carbazole and also show a general resemblance to the absorption of dibenzofuran. However, the bathochromic effect of sulfur is greater than that of oxygen and a small red shift is observed for the dibenzothiophene maxima.^{130, 141}

¹²⁸ K. Kodama, S. Nakatani, K. Umehara, K. Shimizu, Y. Minoda, and K. Yamada, *Agr. Biol. Chem.* **34**, 1320 (1970).

¹²⁹ Z. Yoshida and E. Osawa, *J. Amer. Chem. Soc.* **88**, 4019 (1966).

¹³⁰ F. Momicchioli and A. Rastelli, *J. Chem. Soc. B* 1353 (1970).

^{130a} E. Merkel, *Ber. Bunsenges. Phys. Chem.* **69**, 716 (1965); *Chem. Abstr.* **64**, 170 (1966).

¹³¹ A. D. Walsh, *Quart. Rev.* **2**, 73 (1948).

¹³² G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 3438 (1956).

¹³³ H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

¹³⁴ W. V. Mayneord and E. M. F. Roe, *Proc. Roy. Soc., Ser. A* **152**, 299 (1935).

¹³⁵ E. Sawicki and F. E. Ray, *J. Amer. Chem. Soc.* **74**, 4120 (1952).

¹³⁶ O. Dann and P. Nickel, *Ann. Chem.* **667**, 101 (1963).

¹³⁷ G. V. Gobov, R. N. Nurmukhametov, and L. A. Nakhimovskaya, *Opt. Spektrosk.* **25**, 227 (1968); *Chem. Abstr.* **69**, 82006 (1968).

¹³⁸ G. V. Gobov and L. A. Nakhimovskaya, *Zh. Prikl. Spektrosk.* **7**, 731 (1967); *Chem. Abstr.* **69**, 14409 (1968).

¹³⁹ J. M. Bonnier and P. Jardon, *Compt. Rend. Acad. Sci., Ser. C* **266**, 62 (1968).

¹⁴⁰ J. M. Bonnier, P. Jardon, and J. P. Blanchi, *Bull. Soc. Chim. Fr.*, 4787 (1968).

¹⁴¹ A. Mangini and R. Passerini, *Gazz. Chim. Ital.* **84**, 606 (1954).

The UV spectrum of dibenzothiophene has been determined in solution^{77, 132, 135-146} and shows three main zones of absorption: (A) at 230-265 nm; (B) at 270-285 nm, and (C) at 305-330 nm.^{77, 132, 137, 141, 144, 147} The main absorption band of the entire spectrum occurs in zone A, at 235 nm, which is thus at shorter wavelength than the corresponding band for phenanthrene but of almost identical intensity.¹³² Absorption in zone B is thought to involve a fundamental transition of the B_{1u} type.¹⁴¹ Zone C is as intense for dibenzothiophene as is the long-wavelength absorption of carbazole and is much more intense than that of phenanthrene.¹³² Characterization of dibenzothiophene derivatives has been accomplished by reference to absorption in this band alone¹⁹ and evidence for the existence of a vibronic coupling between dibenzothiophene molecules has been provided from a study of vibrational structure changes in this same region for a dibenzothiophene crystal.¹⁴⁸ Bands in the 250-330 nm range (all three zones) undergo a bathochromic shift of approximately 10 nm in the solid state.¹⁴² The method of magnetophotoselection¹⁴⁹ has been used¹⁵⁰ to determine the polarization of the long-wavelength electronic absorption band of dibenzothiophene.

In the UV spectrum of dibenzothiophene 5,5-dioxide¹³⁶ zones B and C of the dibenzothiophene spectrum are still discernible and the 235 nm band in zone A is resolved into three distinct bands due to activation of the benzenesulfonyl chromophore.¹⁴¹

Sawicki, in 1954, deduced the structure of a number of mono- and disubstituted dibenzothiophenes by spectral comparison with known π -isoelectronic derivatives of carbazole and thereby established the foundations for general structure determination of unknown derivatives of both dibenzothiophene and dibenzoselenophene.^{147, 151} This approach has now been largely replaced by NMR techniques; however, general

¹⁴² T. K. Mukherjee, *J. Phys. Chem.* **74**, 3006 (1970).

¹⁴³ M. J. Kamlet, "Organic Electronic Spectral Data," Vol. 1, p. 433. Interscience, New York, 1960.

¹⁴⁴ R. D. Obolentsev and N. S. Lyubopytova, *Sb. Dokl. Sib. Soveshch. Spektrosk.*, 3rd, 1964, 86 (1966); *Chem. Abstr.* **69**, 6669 (1968).

¹⁴⁵ G. V. Gobov, L. A. Nakhimovskaya, N. S. Proskuryakova, V. S. Tambovtsev and L. N. Ustyugova, *Izv. Akad. Nauk. SSSR, Ser. Fiz.* **32**, 1542 (1968); *Chem. Abstr.* **70**, 24474 (1969).

¹⁴⁶ E. B. McCall, A. J. Neale, and T. J. Rawlings, *J. Chem. Soc.*, 4900 (1962).

¹⁴⁷ E. Sawicki, *J. Org. Chem.* **19**, 1163 (1954).

¹⁴⁸ L. A. Nakhimovskaya, E. G. Ermakova, L. N. Ustyugova, and M. T. Shpak, *Ukr. Fiz. Zh.* **15**, 1034 (1970); *Chem. Abstr.* **73**, 103874 (1970).

¹⁴⁹ S. Siegel and L. Goldstein, Aerospace Corp. Rep. TDR-669 (6250-20)-2 (Dec. 1965).

¹⁵⁰ S. Siegel and H. S. Judeikis, *J. Phys. Chem.* **70**, 2201, 2205 (1966).

¹⁵¹ E. Sawicki, *J. Amer. Chem. Soc.* **77**, 957 (1955).

comments regarding the scope of UV spectroscopy for structural studies may be made. The spectra of most dibenzothiophene derivatives resemble that of the parent in that although functional bands are often superimposed, the three distinct zones usually remain clearly defined.¹⁴⁷ While monomethyl derivatives of dibenzothiophene generally show little change in zone C absorption, 2,8-dimethyl- and 4,6-dimethyldibenzothiophene show bathochromic shifts and 3,7-dimethyldibenzothiophene shows a hypsochromic shift of this zone.⁷⁷ Both 2,8-dibromo- and 3,7-dibromodibenzothiophene show bathochromic shifts of zone C.⁷⁷ Although no clear pattern emerges, the relatively large shifts which occur in the case of the dimethyl compounds are in reasonable accord with shifts calculated from the p-orbital model of dibenzothiophene (Section III,A).⁷⁷ The UV spectra of eleven 2-substituted dibenzothiophenes have been measured and compared with those of the corresponding 2-substituted dibenzofurans.¹⁵² For the dibenzothiophene derivatives studied a linear correlation was shown to exist between the frequency of the main absorption maxima in zone B and the respective Hammett σ_p values. It was concluded that the main differences in the spectra of the compounds studied are due to changes in the electronegativity of the p-orbitals of the heteroatom.

The absence of coplanarity in both 1-phenyl- and 4-phenyldibenzothiophene degenerates their UV spectra to that of dibenzothiophene. In contrast, the main absorption bands of the 2- and 3-phenyl derivatives exhibit the expected bathochromic shift, indicating enhanced conjugation.¹⁴⁶ Available data for the UV absorption of 1,2,3,4-tetraphenyldibenzothiophene is insufficient to correlate with these deductions.¹⁵³

The UV spectra of 2-,^{135, 147} 3-,¹⁵⁴ and 4-nitrodibenzothiophene^{151, 155} and 2,8-dinitrodibenzothiophene^{141, 151} have been recorded. Comparison with the spectrum of 4-nitrodiphenyl sulfide shows that the largest wavelength band for 2-nitrodibenzothiophene, at 334–337 nm,¹⁴⁷ is due to the *p*-nitrothiophenol chromophore. Similarly, the absorption of 4-nitrodibenzothiophene at 375 nm¹⁵¹ is characteristic of an *o*-nitrothiophenol chromophore. The UV absorption spectra of 4-nitro-,¹⁵¹ 4-acetyl-¹⁵¹ and 2-methyl-4-nitrodibenzothiophene¹⁵⁶ are remarkably similar to that of dibenzothiophene itself. This is also true of 2-amino-1-nitrodibenzothiophene, but in this case there is an additional band at 450 nm associated with the *o*-nitroaniline grouping.¹⁵¹ Similarly, bands

¹⁵² M. Kuroki, *Nippon Kagaku Zasshi* **89**, 681 (1968).

¹⁵³ G. Wittig and M. Rings, *Ann. Chem.* **719**, 127 (1968).

¹⁵⁴ E. Sawicki, *J. Org. Chem.* **19**, 608 (1954).

¹⁵⁵ E. Sawicki, *J. Org. Chem.* **18**, 1492 (1953).

¹⁵⁶ F. A. Davis and R. B. Wetzel, *Tetrahedron Lett.* **51**, 4483 (1969).

at 362 and 446 nm in the spectrum of 3-amino-4-nitrodibenzothiophene have been associated with the *o*-nitrothiophenol and *o*-nitroaniline chromophores.¹⁴⁷ The UV spectra of 2-acetyl-,¹⁵¹ 2,8-diacetyl-,¹⁵¹ 3-acetylamino-4-nitro-,¹⁴⁷ 2-amino-3-nitro-,¹⁵¹ 3-amino-7-nitro-,¹⁴¹ 2-amino-8-nitro-,¹⁴¹ 1,2,3,4-tetrahydro-,^{123, 157, 158} 1,2,3,4,4a,9b-hexahydro-¹⁵⁷ and octahydrodibenzothiophene¹⁵⁹ have also been recorded.

Dibenzothiophene acts as a π -electron donor and readily forms complexes with known electron acceptors. In such cases the electronic spectrum of a solution of the two compounds shows a new absorption band, usually in the visible region. The order of donor strengths of several *o,o'*-bridged biphenyls has been estimated from their respective charge-transfer spectra and found to be carbazole > fluorene > dibenzothiophene > dibenzofuran.¹⁶⁰ Dibenzothiophene forms complexes with tetracyanoethylene,^{47, 161} various polynitro derivatives of fluorenone,^{160, 162} naphthalene-1,4,5,8-tetracarboxylic acid dianhydride,⁵⁰ and tetramethyluric acid.⁶¹

The spectrum for the interaction of dibenzothiophene with tetracyanoethylene has been correlated with the calculated highest-occupied orbital energies of dibenzothiophene and used to obtain its ionization potential.¹⁶¹

Electron donation by potential carcinogens, such as 2-acetylamino-dibenzothiophene, has been estimated from the strength of their charge-transfer complexes with chloranil in acetonitrile.^{163, 164} In this context it should be noted that the hydrogen bonding of phenol to the π -electrons of dibenzothiophene has been studied¹²⁹ and that a thiourea adduct has proved useful in the removal of dibenzothiophene from oil.^{20, 63}

5. Luminescence Spectra

The fluorescence spectra of crystalline dibenzothiophene and of solutions of both dibenzothiophene and its sulfone have been recorded

¹⁵⁷ R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. Sect. B* **15**, 573 (1956).

^{157a} B. D. Tilak, *J. Ind. Chem. Soc.* **36** (7) 509 (1959). This is a review lecture of heterocyclic steroids. In this paper, reduction of the 4a,9b-double bond of **68** is stated to lead to cis fusion of rings B and C. The relevant paper is not indexed in *Chemical Abstracts* but is given by Tilak as "Ciporin and Spainhour, *Amer. Petrol. Inst. Res. Project* **48** (23), 21 (1956)."

¹⁵⁸ R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. Sect. B* **15**, 497 (1956).

¹⁵⁹ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.* **62** (1953).

¹⁶⁰ T. K. Mukherjee, *J. Phys. Chem.* **73**, 3442 (1969).

¹⁶¹ A. R. Cooper, C. W. P. Crowne, and P. G. Farrell, *Trans. Faraday Soc.* **62**, 18 (1966).

¹⁶² G. H. Schenk, P. N. Vance, J. Pietrandrea, and C. Mojzis, *Anal. Chem.* **37**, 372 (1965).

¹⁶³ A. C. Allison and T. Nash, *Nature (London)* **197**, 758 (1963).

¹⁶⁴ A. C. Allison, H. E. Peover, and T. A. Gough, *Nature (London)* **197**, 764 (1963).

employing an excitation wavelength of 300 nm.^{45, 136, 140, 165, 166} The spectrum of dibenzothiophene shows a twin peak at ~ 330 nm centered at the wavelength of maximum fluorescence intensity. The fluorescence quantum efficiency, being of the same order as that of thiophene, is considerably less than that of either fluorene or carbazole.^{165, 167} Nevertheless, a combination of fluorescence and phosphorescence has been used^{40, 44, 45} to classify dibenzothiophene systems when concentrations are too low to be detected by IR spectroscopy. Conversely, the fluorescence properties of aryl derivatives of dibenzothiophene 5,5-dioxide have been employed in the detection of X, γ , and corpuscular radiation.¹⁶⁸

The phosphorescence spectrum resulting from transitions between the lowest triplet and singlet ground states of the dibenzothiophene molecule has been determined in a rigid glass and in frozen alkane solutions at liquid nitrogen temperatures.¹⁶⁹⁻¹⁷² With the exception of two IR frequencies at 855 and 563 cm^{-1} , all of the frequencies observed (~ 8) can be explained in terms of Raman transitions.^{169, 173} The band at 855 cm^{-1} is, however, remarkably strong and is considered anomalous.¹⁷³ The lifetime of the luminescence has been visually estimated as 2 seconds,¹⁶⁹ the phosphorescence yield being high relative to that of fluorene.¹⁷⁰ It has been suggested that this increase in yield is due to the heteroatom which reduces the energy difference between the singlet and triplet states of the common, biphenyl nucleus.^{137, 170, 171} The lifetime and quantum yields of triplet state formation have been measured at 25° and interpreted in the context of spin-orbital coupling.^{140, 174-176}

¹⁶⁵ D. W. Ellis and B. S. Solomon, *J. Chem. Phys.* **46**, 3497 (1967).

¹⁶⁶ R. C. Sangster and J. W. Irvine, *J. Chem. Phys.* **24**, 670 (1956).

¹⁶⁷ M. Furst, H. Kallmann, and F. H. Brown, *J. Chem. Phys.* **26**, 1321 (1957).

¹⁶⁸ R. Blank, H. Gold, K. L. Huppert, R. Matejec, R. Raue, and O. Dann, German Patent 1,147,328 (1963); *Chem. Abstr.* **59**, 4719 (1963).

¹⁶⁹ R. C. Heckman, *J. Mol. Spectrosc.* **2**, 27 (1958).

¹⁷⁰ G. V. Gobov and R. N. Nurmukhametov, *Opt. Spektrosk.* **18**, 227 (1965); *Chem. Abstr.* **63**, 1365 (1965).

¹⁷¹ D. N. Shigorin, V. M. Voznyak, G. A. Ozerova, R. N. Nurmukhametov, and A. K. Piskunov, *Proc. Int. Conf. Lumin.*, 1966, **1**, 540 (1968); *Chem. Abstr.* **70**, 52748 (1969).

¹⁷² W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.* **86**, 4537 (1964).

¹⁷³ Y. Kanda, R. Shimada, Y. Gondo, M. Nakamizo, K. Hanada, M. Koyanagi, and Y. Takenoshita, *Proc. Int. Symp. Mol. Struct. Spectrosc.*, 1962 p. B.303 (1963); *Chem. Abstr.* **61**, 1406 (1964).

¹⁷⁴ J. M. Bonnier and P. Jardon, *J. Chim. Phys. Physicochim. Biol.* **67**, 571 (1970).

¹⁷⁵ J. M. Bonnier and P. Jardon, *J. Chim. Phys. Physicochim. Biol.* **66**, 1506 (1969).

¹⁷⁶ J. M. Bonnier and P. Jardon, *J. Chim. Phys. Physicochim. Biol.* **67**, 577 (1970).

The effects of concentration, rate of freezing, and solvent purity on the luminescence spectrum of dibenzothiophene have been studied.^{145, 177, 178} During slow freezing the molecules of the dissolved compound migrate toward the surface of the solvent crystals and thereby decrease the effective concentration.¹⁴⁵ The effect on the triplet-singlet transition of introducing heavy atoms into the system has also been investigated by absorption measurements in benzene and ethyl iodide.^{179, 180}

Although pure biphenyl does not fluoresce, an intense blue phosphorescence is emitted from a crystal of it as 6°K after the addition of dibenzothiophene.¹⁸¹ This phosphorescence originates from energy-trapping centers created in the crystalline lattice adjacent to a dibenzothiophene molecule. The phosphorescence lifetime of a crystal of cyclo-dodecane similarly treated has also been measured.¹⁸²

A novel, short-lived ($< 10^{-6}$ sec) visible luminescence has been observed when dibenzothiophene is excited by an unfocused ruby laser.¹⁸³ The luminescence occurs throughout the visible region and bears no resemblance to either normal fluorescence or phosphorescence. It is thought that a molecular fragmentation is involved which is followed by a chemiluminescent emission.

Photo-induced currents have been measured in dibenzothiophene crystals upon illumination with weakly absorbed light in the 200–400 nm range.^{142, 184, 185} The ratio of surface to bulk currents was measured and correlations made with the applied voltage and the time and intensity of illumination.¹⁸⁵ The surface photo-current peaks followed closely the optical absorption maxima of dibenzothiophene and were largest at ~ 230 and 250 nm.¹⁴² The main step in the generation of charge carriers in dibenzothiophene is believed to be exciton dissociation rather than photoemission. Surface photocurrent peaks of a number of 1:1 charge-transfer complexes of dibenzothiophene have also been compared.¹⁴²

¹⁷⁷ V. A. Butlar and N. A. Kovrizhnykh, *Nekot. Vop. Mol. Fiz. Spektrosk.*, **55** (1967); *Chem. Abstr.* **69**, 91593 (1968).

¹⁷⁸ G. V. Gobov and V. S. Tambovtsev, *Zh. Prikl. Spektrosk.* **9**, 1014 (1968); *Chem. Abstr.* **70**, 72574 (1969).

¹⁷⁹ J. M. Bonnier and P. Jardon, *Compt. Rend. Acad. Sci., Ser. C* **266**, 62 (1968).

¹⁸⁰ J. M. Bonnier and P. Jardon, *J. Chim. Phys. Physicochim. Biol.* **67**, 1385 (1970).

¹⁸¹ A. Bree and R. Zwarich, *Mol. Cryst. Liquid Cryst.* **5**, 369 (1969).

¹⁸² D. J. Morantz and A. C. M. Irons, *Transitions Non Radiat. Mol., Reunion Soc. Chim. Phys.*, **20th**, 158 (1969); *Chem. Abstr.* **74**, 17711 (1971).

¹⁸³ K. B. Eissenthal, W. L. Peticolas, and K. E. Rieckhoff, *J. Chem. Phys.* **44**, 4492 (1966).

¹⁸⁴ P. Chiorboli, S. Piètra, and V. Passalacqua, *Ric. Sci.* **38**, 796 (1968).

¹⁸⁵ L. E. Lyons and G. C. Morris, *J. Chem. Soc.*, 3648 (1957).

6. ESR and EPR Spectra

Radical anions of dibenzothiophene and some of its derivatives have been generated from the parent molecule by the action of potassium in 1,2-dimethoxyethane or tetrahydrofuran at -60° to -70° ,^{76, 186-188} or by using metals such as potassium in liquid ammonia.^{189, 190} These techniques have enabled the electron spin resonance (ESR) spectra of the radical anions of dibenzothiophene,^{76, 186, 188-190} its sulfone,^{191, 192} and some of its methyl derivatives⁷⁶ to be recorded. Hyperfine splitting constants have been assigned to the various protons in the dibenzothiophene molecule and are in accord with LCAO-MO predictions for the *p* model.^{76, 186, 193} (See Section III,A). Spin-density distribution has been calculated⁸² by the unrestricted Hartree-Fock method and has given agreement with experimentally derived data.¹⁸⁸ It has also been calculated using the self-consistent-field MO method, assuming a planar molecule and ignoring *d*-orbital participation in the π -system by the sulfur atom.¹⁹⁴ Coupling constants obtained from these spin density values were also calculated¹⁹⁴ and gave better agreement with experiment than earlier Hückel calculations.⁷⁶ An accurate method for determining coupling constants at low resolution has recently been described.¹⁹⁰

The effect of the sulfone dipole on the ESR spectrum of the dibenzothiophene 5,5-dioxide anion has been examined, modified Hückel calculations which ignored *d*-orbital conjugation predicting spin distributions which agreed with experimental data.¹⁹¹ Proton hyperfine splitting constants have also been obtained for the sulfone.¹⁹² Correlation with MO calculations shows that the sulfone group contributes a vacant symmetric orbital to the conjugated system.¹⁹²

An electron paramagnetic resonance (EPR) study of the anion radicals prepared from the three oxidation states of dibenzothiophene has shown that there is a progressive narrowing of the total EPR spectral widths with increase in the oxidation state of the nucleus.^{187, 195} A progressive decrease in the splitting constants of each pair of protons has also been

¹⁸⁶ R. Gerdil and E. A. C. Lucken, *Proc. Chem. Soc., London*, 144 (1963).

¹⁸⁷ D. H. Eargle, Jr. and E. T. Kaiser, *Proc. Chem. Soc., London*, 22 (1964).

¹⁸⁸ E. G. Janzen, J. G. Pacifici, and J. L. Gerlock, *J. Phys. Chem.* **70**, 3021 (1966).

¹⁸⁹ A. Maximadshy and F. Doerr, *Z. Naturforsch. B* **19**, 359 (1964).

¹⁹⁰ E. Brunner and F. Doerr, *Ber. Bunsenges. Phys. Chem.* **68**, 468 (1964); *Chem. Abstr.* **61**, 10209 (1964).

¹⁹¹ M. M. Urberg and C. Tenpas, *J. Amer. Chem. Soc.* **90**, 5477 (1968).

¹⁹² R. Gerdil and E. A. C. Lucken, *Mol. Phys.* **9**, 529 (1965).

¹⁹³ E. A. C. Lucken, *J. Chem. Soc. A*, 991 (1966).

¹⁹⁴ A. Hinchliffe and N. Trinajstić, *Theor. Chim. Acta* **10**, 458 (1968).

¹⁹⁵ D. H. Eargle, Jr., E. T. Kaiser, and M. M. Urberg, *J. Amer. Chem. Soc.* **88**, 1037 (1966).

found, the constants from dibenzothiophene being in close agreement with those measured by Gerdil and Lucken from the ESR spectrum.¹⁸⁶ One interpretation of these results is that the total spin density located on the aromatic rings of the sulfone anion radical is lowered by the concentration of spin density on the sulfonyl group.¹⁸⁷

The triplet-state, zero-field splitting parameters D and E and the triplet lifetime have been determined from the $\Delta m = \pm 1$ EPR spectra of the photoexcited triplet states of dibenzothiophene and other related compounds using ether glasses cooled to liquid nitrogen temperatures.¹⁵⁰ The values of D and E obtained indicate that sulfur is relatively ineffective in introducing added conjugation to the aromatic rings of the dibenzothiophene molecule and that the ordering of the compounds studies according to increasing conjugation is dibenzothiophene, biphenyl, fluorene, dibenzofuran, carbazole, and phenanthrene.¹⁵⁰ An explanation for the values assumes that the geometry of the triplet state is such that either the two benzene rings are nonplanar or the carbon-carbon bond joining them is buckled. The EPR spectra of dibenzothiophene-Lewis acid complexes¹⁹⁶ and some hydrazyl free radicals¹⁹⁷ of dibenzothiophene have also been recorded.

Proton hyperfine structure at magnetic fields below 100 G in electron magnetic resonance absorptions by oriented triplet dibenzothiophene has been obtained in biphenyl single crystals.¹⁹⁸

7. Physical Dimensions and Crystal Structure

The crystal and molecular structures of sublimed crystals of dibenzothiophene have been determined by established X-ray diffraction techniques.¹⁹⁹ The crystals, which were colorless plates, were monoclinic. The measured bond lengths and angles are shown in Fig. 2, the carbazole numbering system being used for comparative purposes. Variations in the bond lengths of the six-membered ring are observed, with C-10,11 being the longest and C-1,2 and C-3,4 the shortest. Likewise the bond angles within the six-membered rings deviate slightly from 120° , those at C-1 and C-11 being reduced to $\sim 118^\circ$. The C-S bond length of 1.74 \AA is close to the mean value for related conjugated heterocycles.²⁰⁰ The

¹⁹⁶ M. Kinoshita and H. Akamatsu, *Bull. Chem. Soc. Jap.* **35**, 1040 (1962).

¹⁹⁷ R. O. Matevosyan and G. N. Yashchenko, *Zh. Org. Khim.* **4**, 1829 (1968); *Chem. Abstr.* **70**, 28738 (1969).

¹⁹⁸ R. E. Gerkin and A. M. Winer, *J. Chem. Phys.* **51**, 1664 (1969).

¹⁹⁹ R. M. Schaffrin and J. Trotter, *J. Chem. Soc. A*, 1561 (1970).

²⁰⁰ *Chem. Soc. Spec. Publ.* **11**, (1958), **18**, (1965).

²⁰³ L. R. Kronfeld and R. L. Sass, *Acta Crystallogr., Sect. B* **24**, 981 (1968); *Diss. Abstr.* **B28**, 1449 (1967).

C. MISCELLANEOUS REACTIONS AND PROPERTIES OF DIBENZOTHIOPHENE

1. *Thermal Stability*

A condensed thiophene such as dibenzothiophene would be expected²⁰⁴⁻²⁰⁶ to suffer loss of sulfur less readily than would thiophene, which does not undergo measurable thermal decomposition below 500° and only exhibits severe degradation above 800°. ^{207, 208} It is not surprising, therefore, that dibenzothiophene shows a remarkable resistance to thermal degradation. ^{208a, 209, 210} Precise definition of the decomposition point for dibenzothiophene is a difficult task and slight conflict results. In the condensed phase, the decomposition temperature of dibenzothiophene, defined as the temperature at which decomposition occurs at a rate of 1 mole percent per hour, has been estimated²¹¹⁻²¹³ as 545°, and in fact during the pyrolysis of equimolar volumes of benzene and sulfur dioxide in the range 400°-450° small amounts of crystalline dibenzothiophene were isolated together with carbon dioxide and carbon disulfide as the main products of decomposition. ²¹⁴ Dibenzothiophene was found to be the major stable product of the pyrolysis of thianthrene at 550° and is also reported to be stable in the presence of silica chip at temperatures up to 950°, when deep-seated degradation takes place yielding elemental carbon, gaseous products, and a residue which still contains ~ 60% dibenzothiophene. ²¹⁵ Trace quantities of a red sulfur-free

²⁰⁴ R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," p. 50. Interscience, New York, 1960.

²⁰⁵ S. L. Meisel, G. C. Johnson, and H. D. Hartough, *J. Amer. Chem. Soc.* **72**, 1910 (1950).

²⁰⁶ T. J. Wallace and B. Heimlich, *Chem. Ind. (London)* **45**, 1885 (1966).

²⁰⁷ M. G. Rudenko and V. H. Gromova, *Dokl. Acad. Nauk. SSSR* **81**, 207 (1951); *Chem. Abstr.* **46**, 7515 (1952).

²⁰⁸ C. D. Hurd, R. V. Levftan, and A. R. Macon, *J. Amer. Chem. Soc.* **84**, 4515 (1962).

^{208a} E. B. McCall and T. J. Rawlings, British Patent 1,016,373 (1966); *Chem. Abstr.* **64**, 9697 (1966).

²⁰⁹ T. A. Danilova, F. Khalil, I. N. Tits-Skvortsova, A. A. Rybnikova, S. Trippler, M. Shtrobel, E. Ast, G. Bakh, and T. D. Osipenko, *Khim. Seraorg. Soedin. Soderzh. Neftyakh. Nefteprod.* **8**, 170 (1968); *Chem. Abstr.* **71**, 112186 (1969).

²¹⁰ A. J. Hart and A. M. Henke, U.S. Patent 3,095,377 (1963); *Chem. Abstr.* **59**, 6179 (1963).

²¹¹ J. J. Madison and R. M. Roberts, *Ind. Eng. Chem.* **50**, 237 (1958).

²¹² I. B. Johns, E. A. McElhill, and J. O. Smith, *J. Chem. Eng. Data* **7**, 277 (1962).

²¹³ I. B. Johns, E. A. McElhill, and J. O. Smith, *Ind. Eng. Chem., Prod. Res. Develop.* **1**, 2 (1962).

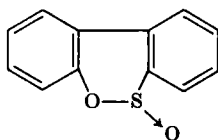
²¹⁴ A. Levy and C. J. Ambrose, *J. Amer. Chem. Soc.* **81**, 249 (1959).

²¹⁵ J. Aitken, T. Heeps, and W. Steedman, *Fuel* **47**, 353 (1968).

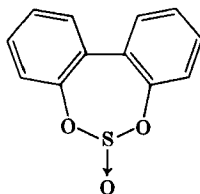
condensed aromatic hydrocarbon were also detected. On the other hand, decomposition of dibenzothiophene over an aluminosilicate catalyst at 400° – 450° , involving formation of hydrogen sulfide as the main product, is claimed to proceed more readily than that of benzothiophene which, in turn, decomposes more readily than thiophene.²⁰⁹ The gas-phase decomposition of dibenzothiophene in the range 350° – 650° yielding benzene and tars has been found to follow first-order kinetics²¹⁶ and 3.2% w/w of catalyst coke is formed when dibenzothiophene vapor is passed over a silica-alumina catalyst at 500° .²¹⁷

A combination of pyrolysis and gas chromatography has been used to separate sulfur compounds of high molecular weight from petroleum fractions and such a method can also be used to produce rapid, reproducible differentiation of such materials.^{3, 36} Pyrolysis of dibenzothiophene, for example, at 500° , gives greater quantities of benzene than is the case for similar pyrolysis of benzothiophene.³⁶ Alkyldibenzothiophenes when similarly treated undergo dealkylation at 400° and degrade at 500° , giving benzene and traces of benzothiophene.³⁶

Elimination of sulfur dioxide from sulfones to form carbon–carbon bonds is known,²¹⁸ and the possibility of formation of biphenylene from dibenzothiophene by this mechanism has therefore been studied.¹⁰⁰ However, pyrolysis at 690° under nitrogen resulted in elimination of SO to give a 95% yield of a 6:1 mixture of dibenzofuran and dibenzothiophene.¹⁰⁰ Elimination of SO also occurs to some extent during electron impact (see Section III, B, 2). The mechanism of the pyrolytic elimination probably involves an intramolecular rearrangement to give the unstable sulfinic ester (15) followed by loss of SO.^{100, 101} In a similar manner, octafluorodibenzofuran is obtained in 72% yield from octafluorodibenzothiophene 5,5-dioxide.¹¹⁰ This mechanism is supported by the recently described pyrolysis of biphenylene 2,2'-sulfite (16) which



(15)



(16)

²¹⁶ A. Levy and C. J. Ambrose, *U.S. Dept. Com., Office Tech. Serv., P.B. Rep. 161498* (1959); *Chem. Abstr.* **55**, 27177 (1961).

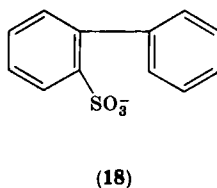
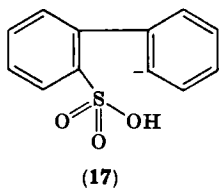
²¹⁷ W. G. Appleby, J. W. Gibson, and G. M. Good, *Ind. Eng. Chem., Process Des. Develop.* **1**, 102 (1962).

²¹⁸ H. Drews, E. K. Fields, and S. Meyerson, *Chem. Ind. (London)*, 1403 (1961).

proceeds via loss of sulfur dioxide to yield dibenzofuran (22%) and via loss of sulfur monoxide to give 1-hydroxydibenzofuran (52%).²¹⁹

2. Chemical Stability

a. *Nucleophilic Attack.* A detailed study of its stability toward nucleophilic attack was not carried out until 1966. Earlier nonreductive techniques for the cleavage of a sulfur-carbon bond in dibenzothiophene were restricted to thermolysis of the sulfone in the presence of basic reagents.¹ Dibenzothiophene was known to be inert,²²⁰ unlike benzo-*thiophene*, in molten potassium hydroxide at 300°, while the sulfone in potassium hydroxide at 200°–250° gave the potassium salt of either biphenyl-2-sulfonic acid²²¹ or 2-hydroxybiphenyl.²²² These observations are consistent with the findings that aliphatic sulfides are usually more stable to alkali than are aliphatic sulfones.²²³ Recently, the decomposition of dibenzothiophene, dibenzothiophene 5-oxide, and dibenzothiophene 5,5-dioxide has been reinvestigated in a white oil-alkali metal hydroxide mixture using both UV spectroscopic and gas chromatographic analyses.^{224, 225} Pyrolysis under these conditions at 300° gave a 100% conversion of the sulfone after 10 minutes, whereas similar treatment of dibenzothiophene and its sulfoxide at 200° for 20 hours gave conversions of 3 and 30%, respectively. In the presence of excess base at 300° the sulfone is almost completely converted to dibenzofuran. The formation of this compound is postulated as proceeding by a reaction sequence in which both 2-phenylbenzenesulfonic acid and 2-hydroxybiphenyl are unstable intermediates.^{64, 225} Small quantities of biphenyl were also detected. The nature of the reaction products virtually demands the initial production of the carbanion **17**, which tautomerizes to the sulfonate ion **18**. The phenolate anion formed by alkaline fusion of **18**



²¹⁹ D. C. DeJongh and R. Y. Van Fossen, *J. Org. Chem.* **37**, 1129 (1972).

²²⁰ R. Weissgerber and C. Seidler, *Chem. Ber.* **60**, 2088 (1927).

²²¹ C. Courtot and C. Chaix, *Compt. Rend. Acad. Sci., Ser. C* **192**, 1667 (1931).

²²² C. Courtot and C. Pomonis, *Compt. Rend. Acad. Sci., Ser. C* **182**, 931 (1926).

²²³ T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Amer. Chem. Soc.* **85**, 2739 (1963).

²²⁴ T. J. Wallace and B. N. Heimlich, *Chem. Ind. (London)* **45**, 1885 (1966).

²²⁵ T. J. Wallace and B. N. Heimlich, *Tetrahedron* **24**, 1311 (1968).

may then undergo intramolecular cyclization to the stable dibenzofuran by loss of sodium hydride.²²⁵ The products from the alkaline treatment of the sulfoxide were similar to those obtained from the sulfone but the additional isolation of dibenzothiophene suggested a disproportionation reaction giving dibenzothiophene and its 5,5-dioxide, which would then decompose in the usual manner.

Treatment of dibenzothiophene with diphenylsilane under reflux for 6 days gave starting material (84%) and tetraphenylsilane (16%). In related heterocycles, such as thianthrene, low yield replacement of sulfur by diphenylsilicon occurs, and in this case the formation of tetraphenylsilane may be indicative of the intermediacy of such an insertion product which then undergoes carbon-carbon bond fission.²²⁶

Nucleophilic substitution in octafluorodibenzothiophene and its dioxide has been described.^{81, 227} Attack by methoxide ion occurs meta to the sulfur atom, giving the 3-methoxy derivative in both cases (Section VI, C, 1).

b. *Electrophilic Attack.* It is well established that electrophilic attack on dibenzothiophene occurs almost exclusively in the 2-position. Only two examples have been encountered where substitution occurs at a different site. The first was the isolation of a small amount of 4-acetyldibenzothiophene along with the 2-acetyl compound from the Friedel-Crafts acetylation of dibenzothiophene,^{228, 229} the second was the isolation of a separable mixture of 2- and 4-dibenzothiophenecarboxaldehyde (3:2) from the related Rieche formylation reaction⁹² (Section VI, F, 1). Unfortunately no specific attempt to isolate possible minor isomers of the various electrophilic substitution reactions of dibenzothiophene has been made. As yields of the 2-isomer are generally good, any other possible isomers have been neglected with the mother liquors upon recrystallization. Oxidation of the sulfur atom to the dioxide is known to cause electrophilic attack to occur in the 3-position^{1, 89} and subsequent reduction³⁵ with LAH can provide a useful route to 3-substituted derivatives.

Although molecular orbital predictions (Section III, A) are often at variance with each other, they are generally agreed that substitution should not take place exclusively at the 2-position. The calculations of Kikuchi⁷² do in fact predict the order $2 > 4 > 3, 1$, which is what is actually observed in the two cases described above.

²²⁶ D. Wittenberg, H. A. McNinch, and H. Gilman, *J. Amer. Chem. Soc.* **80**, 5418 (1958).

²²⁷ R. D. Chambers and J. A. Cunningham, *Chem. Commun.*, 469 (1966).

²²⁸ A. Burger, W. B. Wartman, and R. E. Lutz, *J. Amer. Chem. Soc.* **60**, 2628 (1938).

²²⁹ A. Burger and H. W. Bryant, *J. Org. Chem.* **4**, 119 (1939).

In the absence of any accurate isomer distribution studies the question of theoretical positional reactivities in dibenzothiophene becomes somewhat meaningless. However, when viewed within the context of the behavior of the related heterocycles dibenzofuran, carbazole, and fluorene, specific studies on dibenzothiophene are more valid. Such studies have been made by Eaborn and co-workers. The rates of cleavage of the four isomeric trimethylsilyldibenzothiophenes (Section VI, H, 2) were studied at 50° using a mixture of methanol and aqueous perchloric acid and compared with the rates of protodesilylation of 2- and 4-trimethylsilyldiphenyl sulfide.^{230, 231} The reactivities shown in Fig. 3



FIG. 3. Positional rates of protodesilylation of dibenzothiophene. From Eaborn and Sperry²³⁰.

are relative to that of phenyltrimethylsilane. The reactivity of the 1-position seems somewhat high in the light of observed electrophilic reactions of dibenzothiophene and is probably accounted for by steric acceleration of desilylation by the 9-position. Similarly, 1-, 2-, 3-, and 4-lithiodibenzothiophene were hydrolyzed with tritiated water, yielding the corresponding tritio compounds, and detritiation was studied at 70° using anhydrous trifluoroacetic acid; the positional rates, relative to [³H]₁benzene, determined are shown in Fig. 4.¹⁰⁴ The values shown have been corrected for the 2-position of dibenzothiophene being 6.25, for comparison with Fig. 3.



FIG. 4. Positional rates of protodetritiation of dibenzothiophene. Adapted from Baker and Eaborn¹⁰⁴.

These relative reactivities correlate reasonably well with the observed electrophilic substitution reactions of dibenzothiophene, the 1-position being realistically portrayed by this series of experiments.

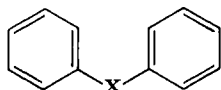
²³⁰ C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).

²³¹ J. A. Sperry, *U.S. Dept. Com., Office Tech. Serv., P.B. Rep.* 145,953 (1959); *Chem. Abstr.* 58, 4592 (1963).

The overall effect of ring formation, e.g., in going from diphenyl sulfide to dibenzothiophene, is a reduction in the reactivity of positions ortho and para to the heteroatom, the reduction usually being greatest for the ortho position.

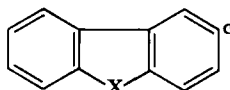
Both sets of experiments indicate a probable order of reactivity $2 > 3 > 4 > 1$ for dibenzothiophene, with the 2-position accounting for over 60% of the total ring reactivity.

Taylor²³² has collected the above and similar data and compared the ratio of reactivities of the ortho and para positions of compounds of type **19** (expressed as $\log f_o : \log f_p$) with the ratio of reactivities of the equivalent positions, *a* and *c*, in compounds of type **20** and found that the latter ratio was lower, i.e., a *relative* increase in the reactivity of the para position (*c*) has occurred upon ring formation. This fall in the ratio $\log f_a : \log f_c$ increases along the series $X = S \ll O (< NH < CH_2)$ in **20**. As this trend parallels the increase in strain in the fused bridging ring it was argued that ring strain was the primary cause of the reduction in ratio. Position *a* is α -aromatic and position *c* is β -aromatic; therefore the above concept represents an extension by Taylor of an earlier explanation of the Mills–Nixon effect in indane.²³³ Further substitution



(19)

$X = CH_2, NH, O, S$



(20)

$X = CH_2, NH, O, S$

in derivatives of dibenzothiophene bearing an electron-withdrawing substituent in the 2-position (e.g., NO_2 , $COCH_3$, succinoyl, Br) always occurs in the 8-position.^{1, 234, 235} No attempt has yet been made to rationalize the position of further substitution in derivatives which have homonuclear directing groups present. Apart from the fact that no clear pattern seems to be emerging, any such attempts will be limited by the fact that the substitution product which is finally obtained pure is possibly dependent upon the crystallization solvent that is being used. The fact that yields are often quite low despite the fact that the reactions generally appear to have gone to completion may well mean that further isomers are present. Various examples of further substitution are dealt with in Sects. VI,A,1; VI,C,2 and 3; VI,D; and VI,E,1 and 2.

²³² R. Taylor, *J. Chem. Soc. B*, 1559 (1968).

²³³ J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron* **21**, 1665 (1965).

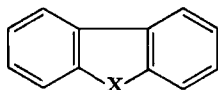
²³⁴ D. D. Gverdsiteli and V. P. Litvinov, *Soobshch. Akad. Nauk Gruz. SSR*, **56**, 105 (1969); *Chem. Abstr.* **72**, 31529 (1970).

²³⁵ H. Gilman and R. K. Ingham, *J. Amer. Chem. Soc.* **75**, 3843 (1953).

The identification of most of these homonuclear further substitution products required a substantial amount of chemical effort; however, the use of NMR spectroscopy in such cases has already proved to be invaluable.^{85,89-92}

3. Oxidation

a. *Chemical Oxidation.* The oxidation of dibenzothiophene with peracetic acid in petroleum ether was reinvestigated when it was found that exclusive formation of either the sulfoxide (**21a**) or the sulfone (**21b**) could be achieved by the correct choice of reaction conditions. The use of a 600% excess of peroxide at 106° gave, after 0.7 hour, a 97% yield of the sulfone (**21b**), while termination of the reaction after 0.07 hour gave the sulfoxide (**21a**) (52%).²³⁶ Oxidation of dibenzothiophene in paraf-



(**21a**) X = SO

(**21b**) X = SO₂

finic white oil with peracetic acid has been studied kinetically at 50°–100°. ²³⁷ The fact that the sulfoxide was oxidized faster than dibenzothiophene was thought to be due to partial dissolution of the sulfoxide in the aqueous phase and the rate-determining step appeared to be attack of a peracetic acid–hydrogen peroxide dimer on the sulfur atom. Ford and Young have investigated the kinetics of the oxidation of dibenzothiophene by peracetic acid using acetic acid/benzene as solvent in the temperature range 15°–60° and in this work obtained yields of sulfoxide of 94%. ²³⁸ The fact that dibenzothiophene was oxidized ~500 times faster than was thiophene under these conditions has been associated with the increased availability of the lone-pair electrons on the sulfur atom of dibenzothiophene, relative to thiophene. Innumerable references to the formation of sulfones of derivatives of dibenzothiophene by peracetic acid oxidation occur but the method is generally the same. ⁷⁶

Oxidation of dibenzothiophene with *t*-butylhydroperoxide proceeded slowly and it was only possible to measure reaction rates in the concentration range 0.3–0.6 mole/liter in acetic acid at 60°. The reaction did not proceed beyond the sulfoxide stage and **21a** was obtained in ~35% yield,

²³⁶ S. R. Sergienko, V. N. Perchenko, and A. A. Mikhnovskaya, *Khim. Sera Azotorg. Soedin., Soderzh. Neftnykh Neft.* **3**, 353 (1960); *Chem. Abstr.* **57**, 10982 (1962).

²³⁷ B. N. Heimlich, and T. J. Wallace, *Tetrahedron* **22**, 3571 (1966).

a free-radical process presumably operating.²³⁸ It is of interest to note here that sulfoxides are known²³⁹ to undergo concurrent oxygen exchange and racemization reactions, such an exchange reaction being invoked to explain why the sulfoxide (**21a**) is recovered almost quantitatively from its solution in excess dinitrogen tetroxide at 0° after 1 hour, without undergoing further oxidation to the sulfone.²³⁹ The kinetics of the oxidation of dibenzothiophene with perbenzoic acid in 1:1 dioxane–water has been studied in the range 0°–40°. In this system the sulfoxide (**21a**) was oxidized approximately 10 times more slowly than the parent compound.²⁴⁰ Oxidation with peroxymaleic acid affords the sulfone (**21b**) (89%).^{240a}

The mechanism of formation of the sulfoxide (**21a**) from dibenzothiophene with chlorine in acetic acid¹ has been studied.²⁴¹ Sodium acetate showed a strong accelerating effect and the results suggested the formation of a dibenzothiophene–chlorine adduct which then decomposed giving the sulfoxide.

Despite the fact that dibenzothiophene can be readily oxidized with peracetic acid, it is generally resistant to milder oxidative conditions. It is, for example, stable to heating in an inert solvent at 150° in the presence of bronze and oxygen, conditions under which both biphenyl sulfide and dibenzyl sulfide gave insoluble precipitates.²⁴² It is not surprising, therefore, that dibenzothiophene has been reported to have little or no antioxidant properties²⁴³ and more recent work has generally confirmed this.^{244–247, 247a} Octahydrodibenzothiophene has, however, been reported to be useful as an oil antioxidant.²⁴⁸

²³⁸ J. F. Ford and V. C. Young, *Amer. Chem. Soc., Div. Petrol. Chem. Preprints* **10**, C111–C112 (1965); *Chem. Abstr.* **66**, 10352 (1967).

²³⁹ N. Kunieda, K. Sakai, and S. Oae, *Bull. Chem. Soc. Jap.* **42**, 1090 (1969).

²⁴⁰ A. Greco, G. Modena, and P. Todesco, *Gaz. Chim. Ital.* **90**, 671 (1960).

^{240a} R. Kavcic and B. Plesnicar, *Bull. Sci. Cons. Acad. RSF Yougoslav.* **10**, 177 (1965); *Chem. Abstr.* **64**, 674 (1966).

²⁴¹ E. Baciocchi and L. Mandolini, *Ric. Sci.* **37**, 863 (1967).

²⁴² Ya. B. Chertkov, V. N. Zrellov, and R. D. Obolentsev, *Khim. Sera Azotorg. Soedin., Soderzh. Neftnykh Neft.* **3**, 461 (1960); *Chem. Abstr.* **56**, 3723 (1962).

²⁴³ G. H. Denison and P. C. Condit, *Ind. Eng. Chem.* **37**, 1102 (1945).

²⁴⁴ G. Fenech, A. Tommasini, and G. Valenti, *Gazz. Chim. Ital.* **92**, 406 (1962).

²⁴⁵ B. Baum and A. L. Perun, *Soc. Plastics Eng. Trans.* **2**, 250 (1962).

²⁴⁶ N. G. Kalantar, *Novosti. Neft. Gaz. Tekhn., Neftepererab. Neftekhim.* **3**, 9 (1962); *Chem. Abstr.* **58**, 11146 (1963).

²⁴⁷ A. J. Hart and A. M. Henke, U.S. Patent 3,095,377 (1963); *Chem. Abstr.* **59**, 6179 (1963).

^{247a} O. L. Harle and J. R. Thomas, *Amer. Chem. Soc., Div. Petrol. Chem. Preprints* **2**, 143 (1957); *Chem. Abstr.* **55**, 6840 (1961).

²⁴⁸ M. F. Sadchikova, D. O. Gol'dberg, and I. M. Makhova, *T. Bashkir. Nauch.-Issled. Inst. Pererab. Nefti* **4**, 119 (1960); *Chem. Abstr.* **56**, 10454 (1962).

Oxidation of dibenzothiophene to the sulfone (**21b**) deactivates the system towards electrophilic attack.²⁴⁹ This appears to be a general property of derivatives of dibenzothiophene. Thus, the sulfones of 1,4-dimethyldibenzothiophene and 6,9-dimethyl-1,2,3,4-tetrahydrodibenzothiophene,²⁵⁰ unlike the parent compounds,^{91, 251} are resistant to attack by the potent formylating agent butyl dichloromethyl ether. Similarly, the sulfone of 1,2,3,4-tetrahydrodibenzothiophene resisted dehydrogenation by chloranil under conditions which rapidly converted octahydrodibenzothiophene to dibenzothiophene,²⁵² and 2-aminodibenzothiophene 5,5-dioxide failed to react with isothiocyanates under conditions in which 2-aminodibenzothiophene gave the corresponding thiourea.²⁵³

The binary system of **21a** and **21b** has been studied and compared with that of the open-chain analogs.²⁵⁴ Both 1,2,3,4-tetrahydrodibenzothiophene 5-oxide and octahydrodibenzothiophene 5,5-dioxide have been studied as engine oil lubricant additives,²⁵⁵ although the preparation of neither of these compounds has been recorded. Dibenzothiophene 5-oxide (**21a**) is reported to be phytotoxic.²⁵⁶

b. *Biological Oxidation.* The isolation of oxidative microbial desulfurizers of petroleum and coal has now been investigated and organisms capable of desulfurizing dibenzothiophene have been identified. The first reported desulfurizing culture was found to be a mixture of *Arthrobacter sp.* and *Pseudomonas sp.*²⁵⁷ attempts to separate the two organisms gave loss of activity. Dibenzothiophene concentrations in excess of 0.6% were found to give reduced desulfurization. Although the only detectable organic products are cellular in nature, it is thought that dibenzothiophene utilization proceeds via initial attack at the thioether linkage followed by cleavage of the benzene rings to give products which then decompose to give CO₂ and H₂O. Eight strains of dibenzothiophene-utilizing bacteria have been isolated from soils, some of which appear to

²⁴⁹ N. M. Cullinane, C. G. Davies, and G. I. Davies, *J. Chem. Soc.*, 1435 (1936).

²⁵⁰ A. N. Fujiwara, E. M. Acton, and L. Goodman, *J. Heterocycl. Chem.* **6**, 389 (1969).

²⁵¹ A. N. Fujiwara, E. M. Acton, and L. Goodman, *J. Heterocycl. Chem.* **6**, 379 (1969).

²⁵² J. D. Loudon, L. B. Young, and A. A. Robertson, *J. Chem. Soc.*, 591 (1964).

²⁵³ V. S. Misra and A. Saxena, *J. Prakt. Chem.* **36**, 256 (1967).

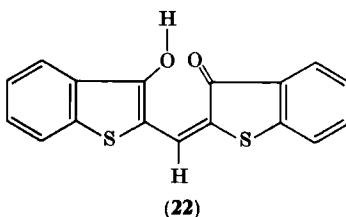
²⁵⁴ N. Marziano and G. Montaudo, *Ann. Chim. (Rome)* **51**, 100 (1961).

²⁵⁵ R. J. Morris, C. N. Thompson, and A. D. Shellard, British Patent 837,725 (1960); *Chem. Abstr.* **54**, 25770 (1960).

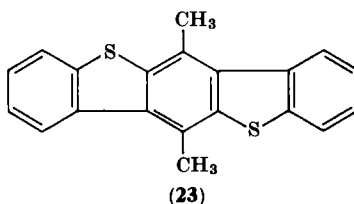
²⁵⁶ A. H. Schlesinger, U.S. Patent 2,624,665 (1953); *Chem. Abstr.* **47**, 6596 (1953).

²⁵⁷ A. T. Knecht, Ph.D. Thesis, Louisiana State University, 1961 [Univ. Microfilms, Order No. 62-1235 (1961)]; *Diss. Abstr.* **22**, 3350 (1962).

be new species of *Pseudomonas*, the names *P. abikonensis* and *P. jianii* being proposed.²⁵⁸ These strains produce sulfur-containing organic acids from dibenzothiophene and approximately 40% of the sulfur present becomes water-soluble upon incubation with either *P. jianii* or *P. abikonensis* for one week. Five water-soluble products have been isolated from conversions using these two strains, three of which have been identified, namely, dibenzothiophene 5-oxide, 3-hydroxy-2-benzo-[b]thiophenecarboxaldehyde, and the hydroxy ketone (22).¹²⁸



Dibenzothiophene incorporated in the diet of rats is eliminated through the urine as 1-hydroxydibenzothiophene 5,5-dioxide and as an unidentified sulfonic acid.²⁵⁹ It is therefore metabolized in a manner similar to that of the carcinogenic benzantracenes,²⁶⁰ involving oxidation of the sulfur atom corresponding to the double band "K-region," coupled with *ortho*-hydroxylation. It has been suggested,²⁵⁹ based on this similarity, that the sulfur atom in selected polycyclic fused thiophenes may bind to protein as does the K-region of the benzantracenes,²⁶⁰ thus explaining the carcinogenic properties of compounds such as 23. Some reservations regarding the structure of the dibenzothiophene metabolite are discussed in Sections IV, A and VI, D.



²⁵⁸ K. Yamada, Y. Minoda, K. Kodama, S. Nakatani, and T. Akasaki, *Agr. Biol. Chem.* **32**, 840, 1205 (1968).

²⁵⁹ R. Y. Ambaye, T. B. Panse, and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. B* **53**, 149 (1961).

²⁶⁰ P. M. Bhargava, H. I. Hadlev, and C. Heidelberger, *J. Amer. Chem. Soc.* **77**, 2877 (1955).

4. Reduction and Desulfurization

Raney nickel in ethanol^{14, 261-264} or dioxane²³⁶ readily desulfurizes dibenzothiophene and many of its derivatives. Quantitative yields of biphenyl are obtained from dibenzothiophene using W7 Raney nickel,²⁶⁵ while Raney cobalt is less effective.²⁶⁶ Treatment of 2-bromodibenzothiophene with Raney nickel gave biphenyl as the only product (31%).²⁶⁷ Rather surprisingly, not even starting material was isolated after treatment of dibenzothiophene 5-oxide or 5,5-dioxide with Raney nickel.²⁶⁷ Desulfurization of octafluorodibenzothiophene with Raney nickel afforded octafluorobiphenyl; however, attempts to prepare octafluorobiphenylene using degassed Raney nickel were unsuccessful.^{81, 110}

The hydrodesulfurization of dibenzothiophene at elevated temperatures and pressures has been studied as a model for the desulfurization of crude oils. Detailed studies involving the following catalysts have been made: Al-Co-Mo,²⁶⁸⁻²⁷⁰ cobalt molybdate,²⁷¹ Ni-W,²⁷² molybdenum sulfide,²⁷³ and the alkali metals, including mixed Na-Rb catalysts.²⁷⁴ The major products of these hydrogenations are biphenyl and hydrogen sulfide, although *o*-phenylthiophenol was isolated using the Na-Rb catalyst. High-pressure reduction of dibenzothiophene using palladium

²⁶¹ G. E. Wiseman and E. S. Gould, *J. Amer. Chem. Soc.* **76**, 1706 (1954).

²⁶² P. Cagniant, D. Cagniant, and M. Mennrath, *Bull. Soc. Chim. Fr.*, 1765 (1964).

²⁶³ L. Reggel, C. Zahn, I. Wender, and R. Raymond, *Bull. U.S. Bur. Mines* **615** (1965); *Chem. Abstr.* **63**, 2804 (1965).

²⁶⁴ K. Dimroth, H. Kroke, and K. Wolf, *Ann. Chem.* **678**, 202 (1964).

²⁶⁵ G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, 3862 (1957).

²⁶⁶ G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.*, 440 (1959).

²⁶⁷ H. Gilman and D. L. Esmay, *J. Amer. Chem. Soc.* **75**, 2947 (1953).

²⁶⁸ R. D. Obolentsev and A. V. Mashkina, *Khim. Sera Azotorg. Soedin., Soderzh. Neft'yakh Neft.*, **3**, 295 (1960); *Chem. Abstr.* **56**, 11537 (1962).

²⁶⁹ R. D. Obolentsev, A. V. Mashkina, A. R. Kuzyev, and G. P. Gribkova, *Khim. Seraorgan. Soedin., Soderzh. Neft'yakh Nefteprod.*, **4**, 166 (1961); *Chem. Abstr.* **57**, 15048 (1962).

²⁷⁰ R. D. Obolentsev and A. V. Mashkina, *Khim. Seraorg. Soedin., Soderzh. Neft'yakh Nefteprod., Dokl. 3-ei (Tre'tei) Nauch. Sessii, Ufa*, 1957, 228 (1959); *Chem. Abstr.* **55**, 6464 (1961).

²⁷¹ R. Papadopoulos and M. J. G. Wilson, *Chem. Ind. (London)*, 427 (1965).

²⁷² S. R. Sergienko and V. N. Perchenko, *Dokl. Akad. Nauk SSSR* **128**, 103 (1959); *Chem. Abstr.* **54**, 1385 (1960).

²⁷³ S. Landa and A. Mrnkova, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv* **11**, 5 (1966); *Chem. Abstr.* **67**, 13492 (1967); *Collect. Czech. Chem. Commun.* **31**, 2202 (1966).

²⁷⁴ S. Friedman, M. L. Kaufman, and I. Wender, *J. Org. Chem.* **36**, 694 (1971); *Amer. Chem. Soc. Div. Fuel. Chem., Preprints* **8**, 209 (1964); *Chem. Abstr.* **64**, 14111 (1966).

on activated charcoal and aluminum chloride in cyclohexane in an atmosphere of hydrogen and hydrogen chloride gases at 150° gave a 53% conversion. The products were shown to be hexahydrodibenzothiophene (37%), other hydrogenated thiophene compounds (4%), and a range of desulfurized compounds (11%).²⁷⁵ Octahydrodibenzothiophene is hydrogenated over a commercial Al-Co-Mo catalyst at approximately the same rate as observed for dibenzothiophene.^{268, 276, 277} Dibenzothiophene is smoothly desulfurized in the vapor phase with hydrogen and palladium.²⁷⁸

Reduction of dibenzothiophene with sodium in liquid ammonia has been shown to be sensitive to the experimental methods employed; however, the major product is usually 1,4-dihydrodibenzothiophene.^{1, 279-281}

The electrochemical reduction of dibenzothiophene in ethylenediamine-lithium chloride solution has been shown to proceed via stepwise reduction of the aromatic nucleus followed by sulfur elimination.^{28, 29} In contrast to the reduction of dibenzothiophene with sodium in liquid ammonia, lithium in ethylenediamine,²⁸³ or calcium hexamine in ether,²⁸² electrolytic reduction produced no detectable thiophenol intermediates. Reduction of dibenzothiophene with calcium hexamine furnished *o*-cyclohexylthiophenol as the major product (77%). Polarographic reduction of dibenzothiophene 5,5-dioxide has shown a four-electron transfer to occur corresponding to reduction of the sulfone group and a further site.⁹

The removal of dibenzothiophene from crude oil has been described earlier (Section II, B).

5. Miscellaneous Properties and Uses

Dibenzothiophene, its sulfoxide, and its sulfone are inactive as anthelmintic agents²⁸³ against *Syphacia obvelata* and *Aspiculuris*

²⁷⁵ E. Aristoff, R. W. Rieve, and H. Shalit, U.S. Patent 3,409,684 (1968); *Chem. Abstr.* **70**, 68005 (1969).

²⁷⁶ R. D. Obolentsev and A. V. Mashkina, *Dokl. Akad. Nauk SSSR* **131**, 1092 (1960); *Chem. Abstr.* **54**, 19131 (1960).

²⁷⁷ R. D. Obolentsev and A. V. Mashkina, *Dokl. Akad. Nauk SSSR* **119**, 1187 (1958); *Chem. Abstr.* **53**, 4876 (1959).

²⁷⁸ C. J. Thompson, H. J. Coleman, R. L. Hopkins, and H. T. Rall, *Amer. Soc. Testing Mater., Spec. Tech. Publ.* **389**, 329 (1965); *Chem. Abstr.* **64**, 15640 (1966).

²⁷⁹ W. Hüchel, S. Gupte, and M. Wartini, *Chem. Ber.* **99**, 1388 (1966).

²⁸⁰ W. Hüchel and I. Nabih, *Chem. Ber.* **89**, 2115 (1956).

²⁸¹ A. J. Birch and D. Nasipuri, *Tetrahedron* **6**, 148 (1959).

²⁸² J. Van Schooten, J. Knotnevus, H. Boer, and P. M. Duinker, *Rec. Trav. Chim. Pays-Bas* **77**, 935 (1958).

²⁸³ W. P. Rogers, J. Cymerman-Craig, and G. P. Warwick, *Brit. J. Pharmacol.* **10**, 340 (1955).

tetraptera, but dibenzothiophene and its derivatives are reported to be strong, nonphytotoxic seed fungicides.²⁸⁴ In this connection dibenzothiophene has found use, over a narrow concentration range, in protecting pine and beech seeds against *Rhizoctonia solani* and *Pythium debaryanum*, both of which are pathogens responsible for the "damping off" of seedlings.²⁸⁵ It has also shown weak inhibition of the rubber tree moldy rot fungus mycelium²⁸⁶ and, in low concentrations, it is useful for the treatment of skin disorders such as acne, dermatoses, seborrhea, and inflammations.²⁸⁷

Dibenzothiophene is stable up to a limit of 425° under neutron bombardment and has therefore been evaluated as an alternative nuclear reactor coolant.^{288, 289} Terphenyl, the normal coolant, is slowly polymerized under electron irradiation and the addition of dibenzothiophene partially stabilizes this polymerization process.²⁹⁰

The absorption of disperse dyes by hydrophobic fibers such as polyesters is increased by the addition of dibenzothiophene 5,5-dioxide to the hot, aqueous dyebath.²⁹¹ Presumably the sulfone behaves as a typical "carrier" acting as a mutual solvent for both fiber and dye.

Dibenzothiophene is one of many compounds studied for scintillation counting behavior.¹⁶⁶ The dielectric properties and dipole moment of dibenzothiophene have been recorded.²⁹²⁻²⁹⁵ Some discrepancy regarding the dipole moment arose in earlier measurements;¹ however, the recent value of 0.84 ± 0.05 D,²⁹²⁻²⁹⁴ as compared with that of 0.53 D possessed by thiophene, agrees with predictions which have been made based on the relative ease of oxidation of these two compounds.¹ The π - and σ -components of the dipole moment have been calculated and found to give an overall moment of 0.93 D,²⁹³ which compares favorably with the experimental value given above. The dipole moments of

²⁸⁴ L. D. Goodhue and C. E. Tissol, U.S. Patent 2,665,234 (1954); *Chem. Abstr.* **48**, 4757 (1954).

²⁸⁵ O. Vaartaja, *Phytopathology* **46**, 387 (1956).

²⁸⁶ G. V. Coles, J. T. Martin, and R. J. W. Bryde, *Long Ashton Agr. Hort. Res. Sta. (Univ. Bristol), Annu. Rep.* 101 (1956); *Chem. Abstr.* **52**, 14064 (1958).

²⁸⁷ Helena Rubinstein Inc., British Patent 916,562 (1963); *Chem. Abstr.* **58**, 13735 (1963).

²⁸⁸ W. W. West, U.S. At. Energy Comm. 4295 (1959); *Chem. Abstr.* **54**, 4184 (1960).

²⁸⁹ R. O. Bolt, B. Fontana, and J. R. Wright, U.S. Patent 2,883,331 (1959); *Chem. Abstr.* **53**, 13825 (1959).

²⁹⁰ H. A. Hartzfeld and R. B. Regier, U.S. At. Energy Comm. IDO-16,839 (1963); *Chem. Abstr.* **59**, 2346 (1963).

²⁹¹ G. B. Robbins, U.S. Patent 3,038,775 (1962); *Chem. Abstr.* **57**, 15389 (1962).

²⁹² A. H. Price, *J. Phys. Chem.* **62**, 773 (1958).

²⁹³ H. Berthod and A. Pullman, *Compt. Rend. Acad. Sci., Ser. C* **262**, 76 (1966).

dibenzothiophene 5-oxide and 5,5-dioxide in benzene, are quoted as 4.41 ± 0.03 and 5.03 ± 0.05 D, respectively.²⁹⁴

The half-wave reduction potentials (HWP) of dibenzothiophene and some of its derivatives have been measured for comparison with those of dibenzofuran and dibenzoselenophene. A shift to more negative HWP was observed for all of the methyl derivatives studied, the magnitude of which depended on the position of substitution. These shifts are in accord with LCAO molecular orbital theory predictions if the sulfur d orbitals are excluded from the calculations (Section III, A).^{77, 192}

IV. Synthesis of Dibenzothiophenes

Dibenzothiophene is now commercially available. However, laboratory preparations from biphenyl, sulfur, and aluminum chloride have continued to be studied, yields of up to 80% being recorded.^{296, 297} The synthesis from biphenyl and hydrogen sulfide in the presence of a catalyst has also been reinvestigated.²⁹⁸

A useful review of methods available up to 1960 for the synthesis of condensed thiophenes, including dibenzothiophene, has been made by Tilak,²⁹⁹ and a similar but shorter review has been made by Mlochowski and Skrzywan.³⁰⁰

Well-established routes to dibenzothiophenes such as reaction of 2,2'-dihydroxy derivatives of biphenyl with phosphorus pentasulfide are still encountered in the literature but have been omitted from the present work as they have already been well documented.¹

²⁹⁴ H. Lumbroso and G. Montaudo, *Bull. Soc. Chim. Fr.*, 2119 (1964).

²⁹⁵ A. L. McClellan, "Tables of Experimental Dipole Moments." Freeman, London, 1963.

²⁹⁶ M. G. Voronkov and F. D. Faitel'son, *Khim. Geterotsikl. Soedin.* **2**, 245 (1967); *Chem. Abstr.* **67**, 90744 (1967).

²⁹⁷ R. D. Obolentsev, S. V. Netupskaya, L. K. Gladkova, V. G. Bucharov, and A. V. Mashkina, *Khim. Seraorgan. Soedin., Soderzh. Neft'akh Nefteprod., Mater. Vtor' Sessii*, 87 (1956); *Chem. Abstr.* **54**, 250 (1960).

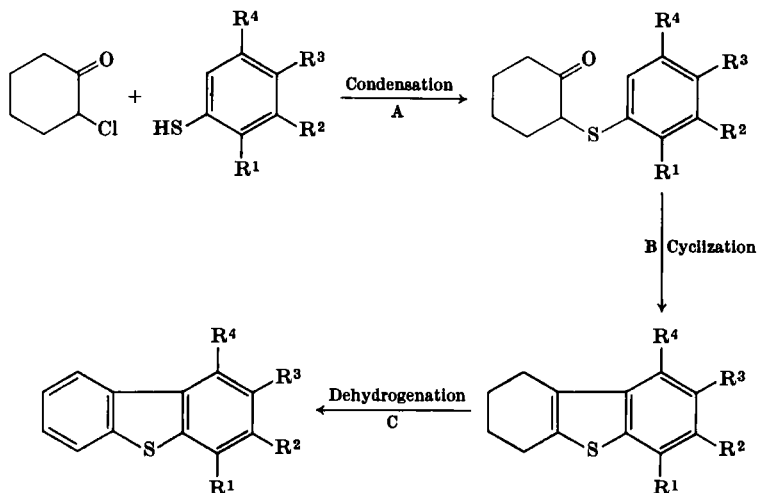
²⁹⁸ J. A. Patterson, R. E. Conary, R. F. McCleary, C. H. Culnane, L. E. Ruidisch, and C. B. Holder, *World Petrol. Congr. Proc. 5th*, (1959) **4**, 309 (1960); *Chem. Abstr.* **58**, 4495 (1963).

²⁹⁹ B. D. Tilak, *Tetrahedron* **9**, 76 (1960).

³⁰⁰ J. Mlochowski and B. Skrzywan, *Wiad. Chem.* **23**, 259 (1969); *Chem. Abstr.* **71**, 52010 (1969).

A. CONDENSATION OF THIOPHENOLS WITH 2-CHLOROCYCLOHEXANONE

The most extensively studied new route to dibenzothiophenes was devised simultaneously by Rabindran and Tilak³⁰¹ and McCall.³⁰² The reaction sequence is illustrated in Scheme 1.



SCHEME 1

The compounds prepared by this route are shown in Table I. Each step has been studied under a variety of conditions and the following points become clear. Step A is best carried out using 2-chlorocyclohexanone, which is more stable than the bromo analog used by Tilak. The use of aqueous sodium hydroxide as the condensing agent has only been employed in the later papers and yields are generally low compared with similar examples where sodium ethoxide or potassium carbonate in acetone are used. The use of pyridine as condensing agent has also been recorded.³⁰³ Step B is usually conducted with phosphorus pentoxide at $\sim 180^\circ$, although phosphoric acid seems to be as efficient and has the advantage that lower temperatures can be employed.

Dehydrogenation of the tetrahydrodibenzothiophene (Step C) was initially carried out using selenium metal at 300° . A separate study of suitable reagents for step C has been made³⁰⁴ in which it was observed that *N*-bromosuccinimide, although giving inferior yields, was effective

³⁰¹ K. Rabindran and B. D. Tilak, *Curr. Sci.* **20**, 207 (1951).

³⁰² E. B. McCall, British Patent 701,267 (1953); *Chem. Abstr.* **49**, 4027 (1955).

³⁰³ G. R. N. Sastry and B. D. Tilak, unpublished work referred to in Tilak.²⁹⁹

³⁰⁴ K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A* **37**, 557 (1953).

TABLE I: SYNTHESIS OF DIBENZOTHIOPHENES BY THE 2-CHLOROCYCLOHEXANONE ROUTE

Substituents on the thiophenol (see Scheme 1)	Yield (%) Step A	Method ^a	Yield (%) Step B	Method ^a	Yield (%) Step C	Method ^a	Derivative of dibenzothiophene formed	Overall yield (%) ^b	Ref.
—	71	C	76	E	40	J	Dibenzothiophene	68	302
	77 ^c	A	74	E	91	K			305
	81	B	88	F	—	—			308
	85	A	66	H	35	L			309
R ¹ = CH ₃	85 ^c	A	62	E	51	K	4-Methyl	71	305
	85	C	70	G	95	K			89
R ² = CH ₃	80 ^c	A	78	E	79	K	3-methyl ^d	48	305
		C	—	E	—	—	3-Methyl + 1-methyl	— ^f	302
R ³ = CH ₃	68 ^c	A	60	E	46	K	2-Methyl	40	305
	90	C	63	E	71	K			302
R ¹ = OCH ₃	77 ^c	D	47	E	30	K	4-Methoxy	11	305
R ³ = OCH ₃	75 ^c	A	low yield	E	—	—	(2-Methoxy) ^e	0	305
R ³ = NO ₂	92 ^c	D	—	—	—	—	(2-Nitro) ^e	0	305
R ¹ = Cl	75	A	56	E	75	I	4-Chloro	31	310
R ³ = Cl	70	C	42	F	15	J	2-Chloro	5	302
R ¹ = R ⁴ = CH ₃	68	D	60	F	85	M	1,4-Dimethyl	35	91
R ¹ = R ⁴ = CH ₃ , R ³ = COOH	49	D	32	F	40	M	1,4-Dimethyl-2-ethoxy- carbonyl (esterified at stage B)	6	91
R ² = OMe	50	D	70	E	30	K	3-methoxy (1?)	10	306

^a Methods: (A) Na/EtOH; (B) K₂CO₃/acetone; (C) NaOH, EtOH/H₂O; (D) NaOH/H₂O; (E) P₂O₅, 180°, (F) H₃PO₄, 100°, 3 hours; (G) H₃PO₄, 200°, 1 hour; (H) P₂O₅, refluxing xylene; (i) NBS, benzoyl peroxide, 75°; (J) chloranil, 24 hours; (K) Se, 300°, 15 hours; (L) S, 230°, 1 hour; (M) Pd/C, 250°–350°.

^b By combination of best intermediate yields.

^c Used 2-bromocyclohexanone.

^d Distilled as an oil; therefore, could be a mixture as found in ref. 302.

^e Not isolated.

^f No yields recorded.

³⁰⁵ K. Rabindran, A. V. Sunthakar, and B. D. Tilak, *Proc. Indian. Acad. Sci., Sect. A* **36**, 411 (1952).

³⁰⁶ M. K. Bhattacharjee and B. D. Tilak, unpublished work referred to in Tilak.²⁹⁹

³⁰⁷ G. N. Rao, B. D. Tilak, and K. Venkataraman, *Proc. Indian. Acad. Sci., Sect. A* **38**, 244 (1953).

³⁰⁸ F. Winternitz, N. J. Antia, M. Tumlivovo, and R. Lachazette, *Bull. Soc. Chim. Fr.*, 1817 (1956).

³⁰⁹ R. Wilputte and R. H. Martin, *Bull. Soc. Chim. Belg.* **65**, 874 (1956).

³¹⁰ R. B. Mitra, K. Rabindran, and B. D. Tilak, *J. Sci. Ind. Res., Sect. B* **15**, 627 (1956).

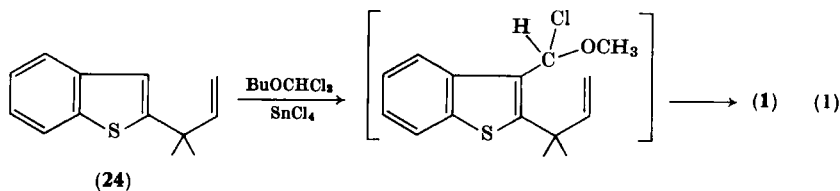
at temperatures as low as 75°. Ortho-substituted thiophenols yield 4-substituted dibenzothiophenes, while para substitution results in the production of 2-substituted compounds. Conflicting reports occur on the use of meta-substituted thiophenols. Tilak³⁰⁵ reports that *m*-thiocresol yields solely 3-methyldibenzothiophene, while McCall³⁰² reports a mixture of 1-methyl- and 3-methyldibenzothiophene which was separable by column chromatography. The fact that the product isolated by Tilak was an oil would indicate that he had in fact similarly isolated a mixture of products. This uncertainty has possible implications in his later recorded reaction of *m*-methoxythiophenol to yield 3-methoxydibenzothiophene as a solid.³⁰⁶ This compound was specifically prepared to prove the structure, by a process of elimination, of 1-methoxydibenzothiophene 5,5-dioxide, the phenol of which was isolated as a metabolite of dibenzothiophene (Section III,C,3). However, it is possible, albeit unlikely, that the synthetic material is 1-methoxydibenzothiophene, which would make the metabolite 3-substituted. The synthesis of 2-methoxydibenzothiophene by this route was abandoned due to a poor yield in step B.³⁰⁵ *p*-Nitrothiophenol condensed readily with the cyclohexanone but failed to cyclize with phosphorus pentoxide.³⁰⁵ In general terms, the reaction works well for thiophenols bearing electron-releasing substituents, but fails, or proceeds in low yield, in the presence of electron-withdrawing groups. There are no recorded examples of substituted 2-chlorocyclohexanones being used. Extension of the reaction in this direction could yield dibenzothiophenes substituted in both rings; in particular, several otherwise difficult formed groupings such as the unknown 2,6-disubstitution pattern should become readily available. The synthesis of benzo-fused dibenzothiophenes by this route has been studied by Tilak.³⁰⁷

B. FROM BENZO[b]THIOPHENES

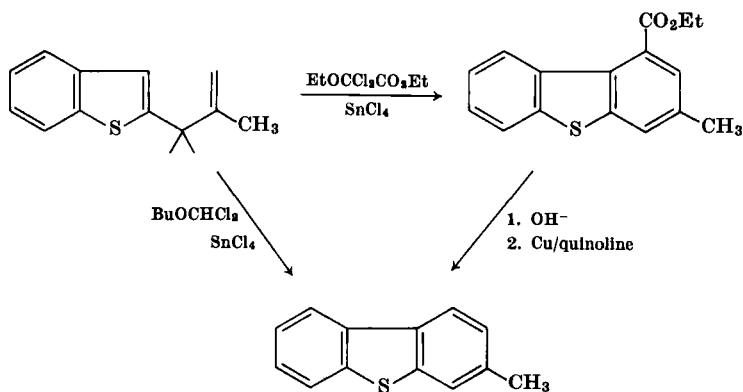
1. *Reaction of Dichloro Ethers with Allylbenzo[b]thiophenes*

Dibenzothiophene has recently been synthesized from 2-allylbenzo[b]thiophene (24) by treatment with dichloromethyl butyl ether and anhydrous stannic chloride at low temperatures, as shown in Eq. (1) (55%).³¹¹ This sequence has been extended by the use of substituted allyl groups and modified formylating agents to yield dibenzothiophenes substituted in the 1-, 1,3-, and 3-positions. For example, treatment of 2-allylbenzo[b]thiophene with the modified formylating agent EtOCCl₂-

³¹¹ J. Ashby, M. Ayad, and O. Meth-Cohn, *Chem. Commun.*, 1251 (1971).



CO_2Et , prepared from diethyl oxalate and phosphorus pentachloride,³¹² yields ethyl 1-dibenzothiophenecarboxylate in high yield. The use of a substituted allyl group is shown in Scheme 2. Extension of this reaction



SCHEME 2

to benzo[*b*]thiophenes substituted in the benzene ring would be interesting; in particular, the use of 4-substituted benzo[*b*]thiophenes would permit the synthesis of 1,9-disubstituted derivatives, only two of which have been reported (Sections IV, C and VI, E, 2).

2. Diels-Alder Reactions

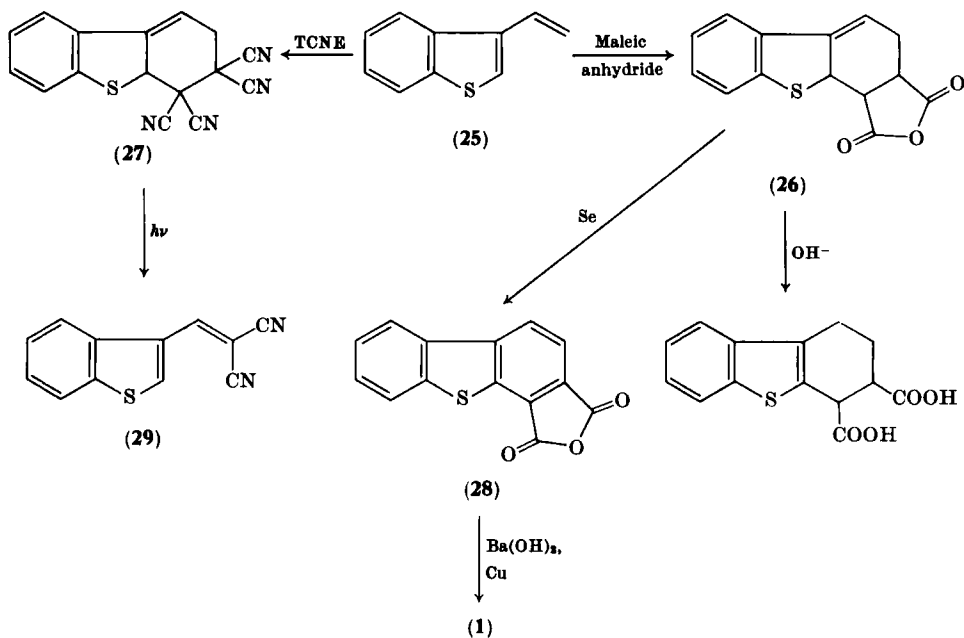
A novel route to reduced dibenzothiophenes bearing substituents in the 3,4-positions has been described involving treatment of 3-vinylbenzo[*b*]thiophene (**25**) with maleic anhydride³¹³ or tetracyanoethylene³¹⁴ to give **26** and **27**, respectively, as shown in Scheme 3.

Compounds **26** and **27** are representatives of the 2,3,4,4a-tetrahydrodibenzothiophene system. As well as being expected from the mode of formation, these structures are further supported by the ability of **26**

³¹² R. E. Jones, *J. Amer. Chem. Soc.* **73**, 5168 (1951).

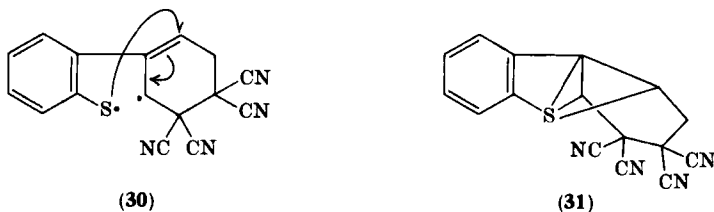
³¹³ W. Davies and Q. N. Porter, *J. Chem. Soc.*, 4961 (1957).

³¹⁴ Q. N. Porter and H. G. Upstill, *Tetrahedron Lett.* **4**, 255 (1972).



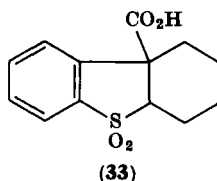
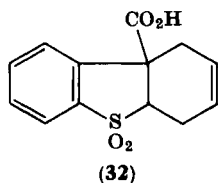
SCHEME 3

and **27** to decolorize bromine water. The 3,4-dicarboxylic anhydride **28** could find useful application in the Friedel-Crafts synthesis of multi-ring fused polycyclics. Photolysis of the adduct (**27**) gives the benzothiophene (**29**).³¹⁴ Skeletal rearrangement must precede the formation of **29**, and this has been postulated to occur either via the diradical **30** or the expanded valence shell intermediate **31**. This type of Diels-Alder reaction has been extended to the synthesis of several other fused thiophene systems.³¹³



The reaction of butadiene with the sulfone of 3-benzo[*b*]thiophene-carboxylic acid under Diels-Alder conditions gives the adduct (**32**). Catalytic reduction over platinum oxide removes the 2,3-double bond,

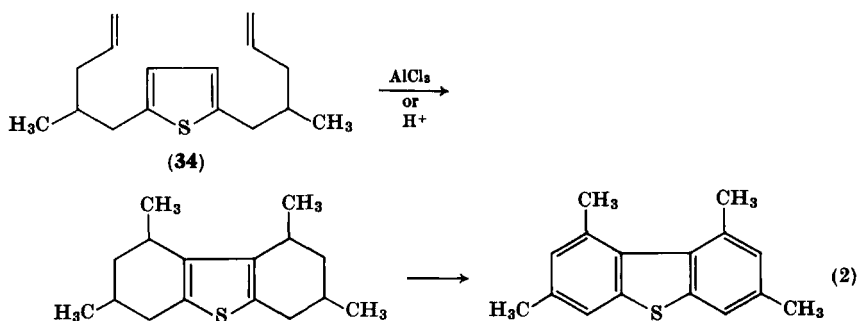
yielding the 1,2,3,4,4a,9b-hexahydro compound (33).³¹⁵ Transformation of the 9b-carboxy group in both 32 and 33 to an amino group and reduction of the sulfone is described in Section VI, E, 2. The availability of a carboxy or amino group on the C-9b carbon means that virtually any functional group can be produced at this site. The Diels–Alder reaction



between three molecules of 3,4-dichlorothiophene-1,1-dioxide to give 2,3,7,8-tetrachlorodibenzothiophene 5,5-dioxide is described in Section VI, C, 2, and the formation of tetraphenyldibenzothiophene from tetracyclone and 2,3-dehydrobenzo[*b*]thiophene is discussed in Section VI, B, 2.

C. FROM THIOPHENES

The total synthesis of dibenzothiophene from thiophene is described in Section V, A.



An elegant synthesis of 1,3,7,9-tetramethyldibenzothiophene has been recorded as shown in Eq. (2).^{95, 316} Cyclization of the diene (34) to the octahydrodibenzothiophene was accomplished with either aluminum chloride or a mixture of acetic acid and sulfuric acid (90%). Subsequent dehydrogenation with palladium on carbon gave the tetramethyl compound. The NMR spectrum of this compound has been discussed earlier

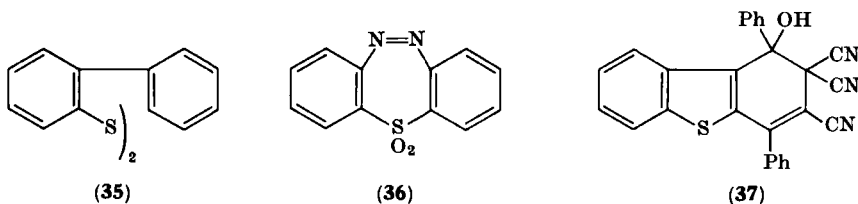
³¹⁵ E. F. Godefroi, U.S. Patent 3,111,527 (1963); *Chem. Abstr.* **60**, 2895 (1964).

³¹⁶ J. Gourier and P. Canonne, *Can. J. Chem.* **48**, 2587 (1970).

(Section III, B, 1). The two methyl groups in **34** were formed from the corresponding methyl esters via reduction to the bis-hydroxymethyl compound followed by ditosylation and reduction with LAH. Both the intermediate diester and the derived dialcohol were separately cyclized to give the corresponding octahydrodibenzothiophenes (50% and 80%, respectively). However, no attempt to dehydrogenate these compounds to the dibenzothiophenes was made. This reaction obviously has considerable potential.

D. MISCELLANEOUS METHODS

Miscellaneous routes to dibenzothiophene include ring closure of the disulfide (**35**) with iodine (64%),³¹⁷ treatment of biphenyl sulfone with



butyllithium to yield the 2,2'-dilithio derivative, which was cyclized with cuprous chloride to a mixture of dibenzothiophene and its sulfone (2:5) (70%),³¹⁸ and the action of phenylsodium³¹⁹ or potassium in dimethoxyethane³²⁰ on biphenyl sulfide. Pyrolysis of 2,3,6,7-dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene 1,1-dioxide (**36**) resulted in nitrogen expulsion to yield dibenzothiophene sulfone and traces of biphenylene, thus indicating the intermediacy of benzyne.³²¹ Low yields of dibenzothiophene have been reported from the catalytic dehydrocyclization of biphenyl sulfide,³²² from treatment of biphenyl sulfoxide with sodium hydroxide at 300°, ³²⁵ from the cyclization of *o*-bromobiphenyl sulfide with methylmagnesium iodide and cobalt chloride,³²³ and as a by-product in the high-temperature catalytic synthesis of benzo[*b*]thiophene

³¹⁷ E. Campaigne, L. Ergener, and B. G. Heaton, *J. Org. Chem.* **27**, 411 (1962).

³¹⁸ V. N. Gogte, V. S. Palkar, and B. D. Tilak, *Tetrahedron Lett.* **6**, 30 (1960).

³¹⁹ A. Lüttringhaus, G. Wagner-V. Sääf, E. Sucker, and G. Borth, *Ann. Chem.* **557**, 46 (1945).

³²⁰ R. Gerdil and E. A. C. Lucken, *J. Chem. Soc.*, 5444 (1963).

³²¹ G. Wittig, and H. F. Ebel, *Ann. Chem.* **650**, 20 (1961).

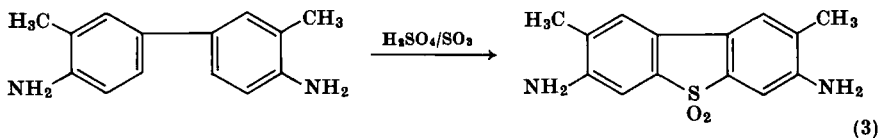
³²² S. Trippler, T. A. Danilova, and A. F. Plate, *Neftekhimiya* **10**, 273 (1970); *Chem. Abstr.* **73**, 35139 (1970).

³²³ G. Nespoli and M. Tiecco, *Bol. Sci. Fac. Chim. Ind. Bologna, Suppl.* **24**, 239 (1966); *Chem. Abstr.* **67**, 73467 (1967).

from thiophenol and acetylene.³²⁴ Thianthrene gives a small quantity of dibenzothiophene when heated with copper powder at 300°. ^{325, 326} Replacement of the copper with degassed Raney nickel³²⁷ again yields dibenzothiophene (12%) and traces of triphenylene, a product usually taken as being indicative of benzyne participation.³²⁸ It therefore seems likely that simultaneous expulsion of both of the sulfur atoms of the thianthrene molecule occurs to some extent. Reaction of 2-benzyl-3-benzoylbenzo[*b*]thiophene with tetracyanoethylene yields **37**, the only recorded derivative of 1,2-dihydrodibenzothiophene.³²⁹ Sulfur extrusion from dibenzo[*c,e*]dithiins, yielding dibenzothiophenes, is discussed in Section VI, A, 2.

Dibenzothiophene has been isolated in low yield from the pyrolysis of benzene and sulfur dioxide in glass ampuls at between 400° and 540° and the reaction kinetics determined.²¹⁴

The Friedel-Crafts cyclization of biphenyl-2-sulfonyl chloride to give dibenzothiophene sulfone has been described (55%);^{309, 325} however, thermal cyclization in octachloronaphthalene at 250°, under nitrogen, is reported to yield dibenzothiophene itself rather than the sulfone (47%).^{208a} Reaction of biphenyl compounds with oleum (H₂SO₄ + SO₃) to yield derivatives of dibenzothiophene 5,5-dioxide is widely used for the preparation of dyestuff intermediates (Section VI, E, 2). A typical example is shown in Eq. (3), starting from *o*-tolidine.³³⁰



The synthesis of 2,7-dinitrodibenzothiophene via cyclization of the biphenyl derivative (**38**) with bromine, at 200°, ³³¹ could be usefully extended to the synthesis of other deactivated dibenzothiophenes. The 2,7-disubstitution pattern is rare, the only other reference to it being the

³²⁴ T. Lesniak, *Rocz. Chem.* **38**, 1923 (1964); *Chem. Abstr.* **62**, 9090 (1965).

³²⁵ W. L. F. Armarego and E. E. Turner, *J. Chem. Soc.*, 1665 (1956).

³²⁶ R. Passerini and G. Purrello, *Ann. Chim. (Rome)* **48**, 738 (1958).

³²⁷ G. M. Radger, P. Cheuychit, and W. H. F. Sasse, *Aust. J. Chem.* **17**, 336 (1964).

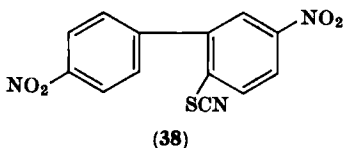
³²⁸ J. D. Roberts, H. E. Simmons, L. A. Carlsmith, and C. W. Vaughan, *J. Amer. Chem. Soc.* **75**, 3290 (1953).

³²⁹ American Cyanamid Co., Neth. Application 6,509,177 (1966); *Chem. Abstr.* **66**, 2490 (1967).

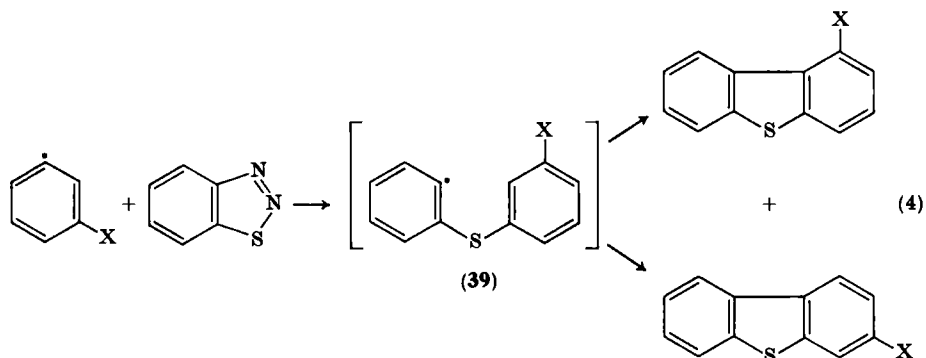
³³⁰ Ciba Ltd., British Patent 773,617 (1957); *Chem. Abstr.* **51**, 15587 (1957).

³³¹ F. Bottino and R. Passerini, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania* [4] **3**, 471 (1957); *Chem. Abstr.* **52**, 9997 (1958).

nitration of 2-bromodibenzothiophene-5,5-dioxide, which was assumed, probably correctly, to have occurred in the 7-position.²³⁵ Phenyl radicals

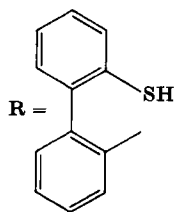
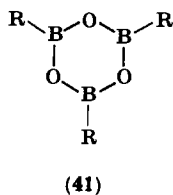
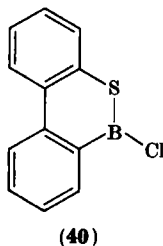


generated from *N*-nitrosoacetanilides have been found to attack 1,2,3-benzothiadiazole to yield derivatives of dibenzothiophene,³³² as shown in Eq. (4). The reaction has been carried out where X = H, CH₃, or OCH₃. The intermediate radical (39) can give the observed products



via intramolecular homolytic substitution; furthermore, the product isomer distribution is identical to that formed as a result of independent generation of **39** by aprotic diazotization of 2-aminophenyl-3'-X-phenyl sulfide, thus confirming the proposed reaction mechanism.

Finally, dibenzothiophene has been isolated in moderate yields from hydrolysis of either **40** or **41** (33% and 70%, respectively).³³³ Both of these compounds were formed in good yield from *o*-mercaptobiphenyl. However, the general synthetic significance of this reaction is not yet clear.



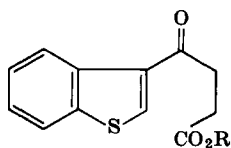
³³² L. Benati, A. Tundo, and G. Zanardi, *Chem. Commun.*, 590 (1972).

³³³ F. A. Davis and M. J. S. Dewar, *J. Amer. Chem. Soc.* **90**, 3511 (1968).

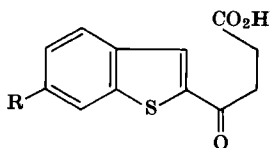
V. Ring-Reduced Dibenzothiophenes

A. RING KETONES

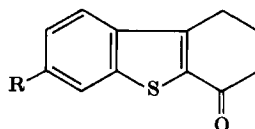
Cagniant and Cagniant³³⁴ have reported that succinoylation of benzo[*b*]thiophene under Friedel–Crafts conditions yields a separable mixture of the γ -ketobutyric acids **42a** and **43a** in a ratio of 9:1 (combined yield 85%). Huang–Minlon reduction of **42a** to the butyric acid (90%) followed by cyclization of the derived acid chloride (90%) was reported to yield 4-keto-1,2,3,4-tetrahydrodibenzothiophene (**44a**) (69% overall). Likewise, acylation of benzo[*b*]thiophene with the ester chloride of succinic acid in carbon disulfide–aluminum chloride gave a separable mixture (80%) of the 2- and 3- γ -ketobutyric esters. Two alternative



(42a) R = H

(42b) R = CH₃

(43a) R = H

(43b) R = OCH₃

(44a) R = H

(44b) R = OCH₃

routes to **44a** have been devised by subsequent workers^{158, 335–337} due to low yields being obtained during attempts to repeat the initial succinoylation. Reproducibly high yields of the keto ester (**42b**) have been obtained by acylation of benzo[*b*]thiophene in benzene with the ester chloride of succinic acid using anhydrous stannic chloride as catalyst.^{158, 336, 337} Huang–Minlon reduction of **42b** was accompanied by ester hydrolysis yielding the corresponding γ -(3-benzo[*b*]thienyl)butyric acid. Cyclization as described above yields **44a** in overall yield of ~45%. Alternatively the keto acid (**42a**) can be formed by reaction of the Grignard reagent from 3-bromobenzo[*b*]thiophene with succinic anhydride (66%) leading to **44a** as described above (overall yield 57%).³³⁵ Attempts to cyclodehydrate the diketone **45** to **44a** using several dehydrating agents were unsuccessful.¹⁵⁸

The low yield of **43a** from the succinoylation of benzo[*b*]thiophene³³⁴ precluded a synthesis of **46** from this keto acid; however, an alternative

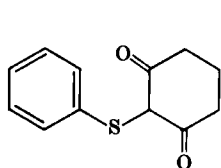
³³⁴ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 336 (1952).

³³⁵ R. J. Collins and E. V. Brown, *J. Amer. Chem. Soc.* **79**, 1103 (1957).

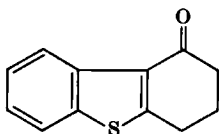
³³⁶ E. Campaigne, D. McClure, and J. Ashby, *J. Heterocycl. Chem.* **6**, 771 (1969).

³³⁷ R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. Sect. B* **14**, 132 (1955).

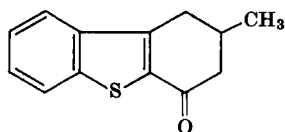
approach to the synthesis of γ -(2-benzo[*b*]thienyl)butyric acid has been described involving condensation of diethyl malonate with 2-(2'-chloro-ethyl)benzo[*b*]thiophene followed by hydrolysis and decarboxylation.³³⁸



(45)



(46)

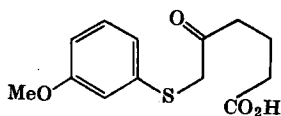


(47)

Cyclization of this acid with stannic chloride in carbon disulfide gave 1-keto-1,2,3,4-tetrahydrodibenzothiophene (**46**) (65%). The 2-methyl analog of **46** has likewise been synthesized from diethyl methylmalonate.³³⁸

Condensation of 3-chloromethylbenzo[*b*]thiophene with diethyl malonate followed by hydrolysis, decarboxylation, Arndt-Eistert homologization, hydrolysis, and cyclization of the derived acid chloride with anhydrous stannic chloride yielded 2-methyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene (**47**).³³⁹

7-Methoxy-4-keto-1,2,3,4-tetrahydrodibenzothiophene (**44b**), an intermediate in the synthesis of 6-thiaisoequilenin,^{340, 341} was prepared by condensation of *m*-methoxythiophenol with 6-chloro-5-ketocaproate in pyridine, yielding the intermediate **48**. Cyclodehydration of **48** in polyphosphoric acid gave the corresponding 3-benzo[*b*]thienylbutyric acid, which was cyclized to **44b** using acetic anhydride and zinc chloride (overall yield 48%).³⁴² Succinoylation of 6-methoxybenzo[*b*]thiophene occurs predominantly in the 2-position, yielding the keto acid (**43b**).³⁴²



(48)

Reduction of the ketones **44a** and **46** with sodium borohydride gave the secondary alcohols **49** and **50**, respectively, in high yield.³³⁸

³³⁸ D. Cagniant and G. Kirsch, *Compt. Rend. Acad. Sci. Ser. C* **72**, 948 (1971).

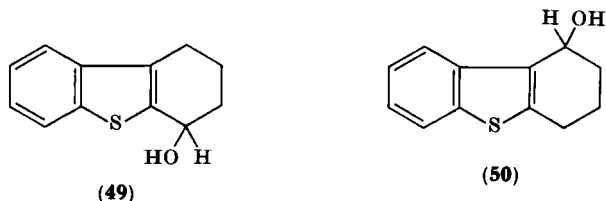
³³⁹ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 185 (1953).

³⁴⁰ B. D. Tilak and M. K. Bhattacharjee, *Indian J. Chem.* **7**, 36 (1969).

³⁴¹ B. D. Tilak and M. K. Bhattacharjee, *J. Indian Chem. Soc.* **36**, 509 (1959).

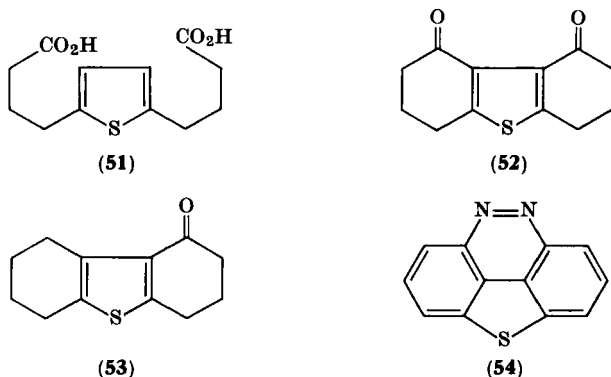
³⁴² M. K. Bhattacharjee, R. B. Mitra, B. D. Tilak, and M. R. Venkiteswaren, *Tetrahedron* **10**, 215 (1960).

The total synthesis of dibenzothiophene from thiophene³⁴³ has made available two ketones of potential synthetic interest. Stepwise succinylation and reduction of thiophene in the 2- and 5-positions gave the



diacid (**51**). Double cyclization of **51** using phosphorus pentachloride in conjunction with anhydrous stannic chloride or aluminum chloride gave 1,9-diketo-1,2,3,4,6,7,8,9-octahydrodibenzothiophene (**52**) (40–60%). Alternatively, monocyclization of **51** (74%) with phosphoric acid, followed by Huang–Minlon reduction and cyclization of the derived butyric acid yielded the ketone **53**. Dibenzothiophene was obtained from both **52** and **53** via reduction and dehydrogenation. Both of the ketones (**52** and **53**) should enable substituents to be introduced to the relatively inaccessible 1- and 1,9-positions. Moreover the diketone (**52**) could be used to bridge the 1,9-positions of dibenzothiophene; hydrazine, for example, could lead to **54**.

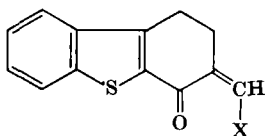
The valuable synthetic intermediate 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrodibenzothiophene (**55a**) has been prepared from the 4-keto compound (**44a**) by treatment with sodium methoxide and ethyl



formate (97%)^{158, 335} or with sodium hydride and methyl formate (73%).³³⁶ The melting point of the material varied reversibly with the solvent (126°–127° from ethanol, 114°–116° from dioxane).

³⁴³ A. U. Rahman and O. L. Tombesi, *Tetrahedron Lett.* **36**, 3925 (1968).

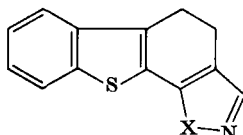
Reaction of **55a** with thionyl chloride gave the 3-chloromethylene compound (**55b**) (62%) and with isopropyl iodide the 3-isopropoxymethylene derivative (**55c**) (57%).³³⁶ Hydroxylamine condenses with



(**55a**) X = OH

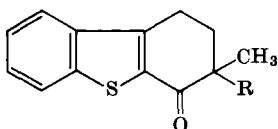
(**55b**) X = Cl

(**55c**) X = O-i-Pr



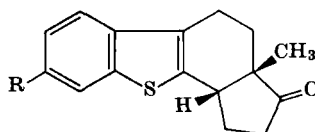
(**56a**) X = O

(**56b**) X = NH



(**57a**) R = CN

(**57b**) R = CO₂Me



(**58a**) R = H

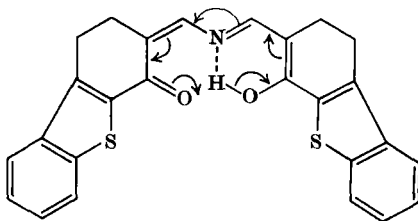
(**58b**) R = OH

55a, yielding the isoxazole (**56a**) (88–96%) which upon cleavage with sodium methoxide followed by alkylation gives 3-cyano-3-methyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene (**57a**) (77–91% from **55a**).^{158, 335} Likewise hydrazine reacts with **55a** yielding the pyrazole (**56b**) (53%), which upon catalytic dehydrogenation gives 1*H*-benzo[*b*]thieno[3,2-*g*]indazole (73%).³³⁶ Treatment of **44a** with sodium methoxide and dimethyl carbonate followed by *in situ* methylation gave **57b** (83%).³⁴⁴ The Reformatsky ester derived from **57b** has been used as the starting material for the synthesis of 3-desoxy- β -nor-6-thiaisoequilenin (**58a**).³⁴⁴ Similarly, from the methoxy ketone (**44b**), β -nor-6-thiaisoequilenin (**58b**) has been synthesized.^{340, 341} The cyano compound (**57a**) had been utilized by two groups in an earlier, nonstereospecific synthesis of 3-desoxy- β -nor-thiaequilenin as two stereoisomeric *dl* pairs.^{157a, 158, 335, 337}

Reaction of the 7-methoxyketone (**44b**) with the appropriate reagents as described above for **44a** gave the 7-methoxy analogs of **55a** (99%), **56a** (70%), and **57a** (78%).³⁴²

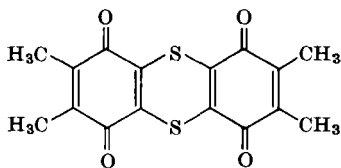
Ammonium acetate in acetic acid converts **55a** into the imine (**59**). The hydrogen-bonded, resonance-stabilized form shown is consistent with its high melting point and intense color. The structure is further supported by the ability of the naphthalene analog, which is more soluble, to form a stable complex with cupric perchlorate.³³⁶

³⁴⁴ B. D. Tilak, V. N. Gogte, A. S. Jhina, and G. R. N. Sastry, *Indian J. Chem.* **7**, 31 (1969).

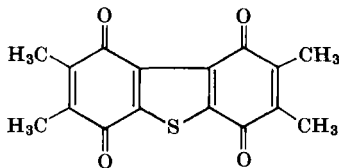


(59)

Treatment of 5,6-dichloro-2,3-dimethyl-*p*-benzoquinone with sodium sulfide followed by oxidation with nitric acid yields the thianthrene derivative (60). Sulfur extrusion from 60 with peracetic acid leads to 2,3,7,8-tetramethyl-1,4,6,9-dibenzothiophene tetrone (61) (overall yield 57%).³⁴⁵



(60)



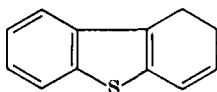
(61)

The synthesis of a substituted derivative of 2-keto-1,2,3,4-tetrahydrodibenzothiophene is discussed in Section VI, D.

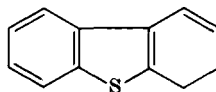
B. HYDRODIBENZOTHIOPHENES

1. Dihydrodibenzothiophenes

Reduction of 4-keto-1,2,3,4-tetrahydrodibenzothiophene (44a) with sodium borohydride followed by dehydration of the resultant carbinol by vacuum distillation in the presence of a trace of PPA yields 1,2-dihydrodibenzothiophene (62) as a low-melting solid. Similarly, 3,4-dihydrodibenzothiophene (63) has been prepared from the 1-keto compound (46) as an unstable liquid.³³⁸



(62)



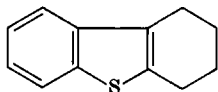
(63)

³⁴⁵ K. Fickentscher, *Chem. Ber.* **102**, 1739 (1969).

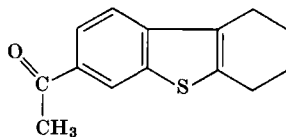
The reduction of dibenzothiophene with sodium in liquid ammonia to give a dihydro compound, probably 1,4-dihydrodibenzothiophene, has been discussed in Section III, C, 4. A highly substituted 1,2-dihydrodibenzothiophene (**37**) has also been described (Section IV, D).

2. Tetrahydrodibenzothiophenes

Cyclodehydration of 2-phenylthiocyclohexanone with a variety of reagents yielding 1,2,3,4-tetrahydrodibenzothiophene (**64**) as an oil has been reported,^{262, 302, 308, 309, 334} and represents the simplest way of obtaining this material (88%). Alternatively, reduction of 4-keto-1,2,3,4-tetrahydrodibenzothiophene under Huang–Minlon conditions affords **64** in high yield.³³⁴ Trace amounts of **64** were detected in the reduction of dibenzothiophene with calcium hexamine and during electrolysis in ethylenediamine–lithium chloride solution (Section III, C, 4). Peracetic acid oxidizes **64** to its sulfone (65%),^{157, 252, 308} which is readily reduced to **64** again with LAH.^{252, 308} The value of 1,2,3,4-tetrahydrodibenzothiophene 5-oxide as a lubricating oil additive has been described but no details of its preparation or physical properties were given.²⁵⁵



(64)



(65)

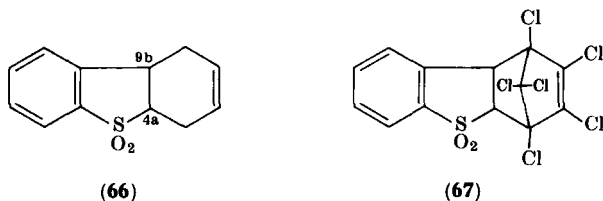
Several substituted derivatives of **64** have been prepared in high yield during the synthesis of dibenzothiophenes via the 2-chlorocyclohexanone route (Section IV, A), namely, 8-methyl-,^{302, 305} 7-methyl-,³⁰⁵ 6-methyl-,^{89, 305} 8-methoxy-,³⁰⁵ 7-methoxy-,³⁰⁶ 6-methoxy-,³⁰⁵ 8-chloro-,³⁰² 6-chloro-,³¹⁰ 6,9-dimethyl-,⁹¹ and 6,9-dimethyl-8-ethoxycarbonyl-1,2,3,4-tetrahydrodibenzothiophene.⁹¹

Friedel–Crafts acetylation of **64** gives a monoacetyl derivative (85%) originally formulated as 8-acetyl-1,2,3,4-tetrahydrodibenzothiophene.³³⁴ Subsequent work^{262, 123} revealed that it was in fact the 7-acetyl compound (**65**). The structure was established via reduction of the acetyl group to 7-ethyl-1,2,3,4-tetrahydrodibenzothiophene (93%) followed by desulfurization to *p*-ethylphenylcyclohexane. Compound **65** undergoes the Pfitzinger reaction with 5-methylisatin.³³⁴

Diels–Alder condensation of benzo[*b*]thiophene 5,5-dioxide with butadiene or hexachlorocyclopentadiene yields the adducts **66** and **67**, respectively, examples of the 1,4,4a,9b-tetrahydrodibenzothiophene

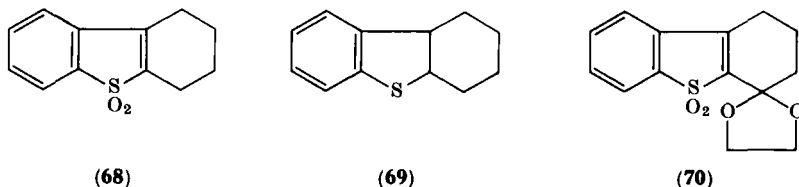
ring system.³⁴⁶ The related formation³¹⁵ of 1,4,4a,9b-tetrahydrodibenzothiophenes bearing a substituent on the C-9b carbon atom is described in Sections IV, B, 2; VI, E, 2; and VI, G, 1.

Two examples of the 2,3,4,4a-tetrahydrodibenzothiophene system have been described earlier (Section IV, B, 2).



3. Hexahydrodibenzothiophenes

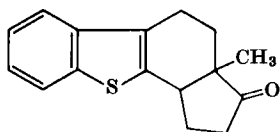
The 4a,9b double bond in 1,2,3,4-tetrahydrodibenzothiophene 5,5-dioxide (**68**) and similar compounds, is essentially nonaromatic and in this respect resembles the 2,3 bond in benzo[*b*]thiophene 1,1-dioxide.⁶⁶ Catalytic reduction of **68** results in the formation of 1,2,3,4,4a,9b-hexahydrodibenzothiophene 5,5-dioxide (92%). Subsequent reduction of the sulfone with LAH yields 1,2,3,4,4a,9b-hexahydrodibenzothiophene (**69**) as an oil (78%).^{157, 157a} Oxidation of 4-keto-1,2,3,4-tetrahydrodibenzothiophene (**44a**) to its sulfone with peracetic acid (63%) followed by



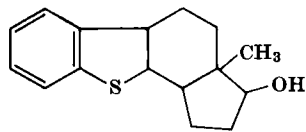
treatment with ethylene glycol and *p*-toluenesulfonic acid gives the ketal (**70**) (76%), catalytic reduction of which again results in reduction of the 4a,9b bond (35%).¹⁵⁷ Reduction of the 4a,9b double bond in tetrahydrodibenzothiophene 5,5-dioxides with palladium on carbon seems to be of general application; thus the sulfur analog (**72**) of 3-desoxyestradiol has been synthesized from one isomer of the equilenin analog (**71**) via sulfone formation, catalytic hydrogenation, and chemical reduction of the sulfone and ketone functions (12% overall three steps, mixture of isomers).^{157, 157a}

³⁴⁶ O. C. Elmer, U.S. Patent 2,664,426 (1953); *Chem. Abstr.* **49**, 1106 (1955).

The formation of 1,2,3,4,4a,9b-hexahydrodibenzothiophenes bearing a substituent on the C-9b carbon atom is described in Sections IV, B,2; VI, E,2; and VI, G,1.



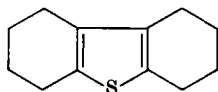
(71)



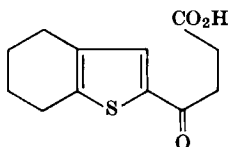
(72)

4. Octahydrodibenzothiophenes

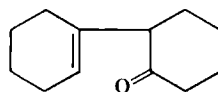
1,2,3,4,6,7,8,9-Octahydrodibenzothiophene (**73**) has been prepared by the following sequence.³³⁴ Friedel-Crafts acylation of 4,5,6,7-tetrahydrobenzo[*b*]thiophene with succinic anhydride (87%) or with the ester chloride of succinic acid followed by hydrolysis (80%), yields the keto acid (**74**). Huang-Minlon reduction of **74** followed by cyclization of the derived acid chloride with stannic chloride yields 1-keto-1,2,3,4,6,7,8,9-octahydrodibenzothiophene (**53**) (Section V, A). Reduction of **53** gives **73** as a solid (overall yield 32%).



(73)



(74)



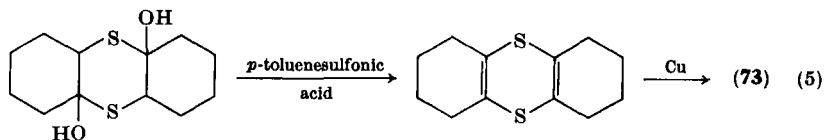
(75)

Several less tedious ways of preparing **73** are now available. Refluxing cyclohexanone with sulfur under nitrogen yields a mixture of **73** (10%) and the intermediate 2-cyclohex-1'-enylcyclohexanone (**75**) (5%) after distillation.³⁴⁷ Treatment of **75** with sulfur under reflux again yields **73** (45%). Although the yields are poor in this synthesis the availability of the starting materials and the ease of the reaction make it an attractive route. A modification of the above route involving the addition of aluminum chloride has been reported.²⁹⁷ Alternatively **73** has been prepared by reduction of the potassium salt of the enol tautomer of thiacyclohexanone with *N*-bromosuccinimide in benzene (41%).³⁴⁸ The preparation of **73** from perhydro-4a,9a-dihydroxythianthrene has been accomplished in 74% yield²⁵² by the sequence shown in Eq. (5). The reduction of 1,9-diketo-1,2,3,4,6,7,8,9-octahydrodibenzothiophene (**52**) to **73** has been described earlier (Section V, A).

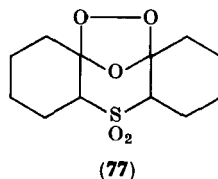
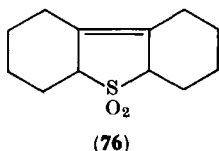
³⁴⁷ W. Cooper, *J. Chem. Soc.*, 1386 (1955).

³⁴⁸ J. Morgenstern and R. Mayer, *J. Prakt. Chem.* **34**, 116 (1966).

Treatment of **73** with selenium metal at 360° yields dibenzothiophene.³⁴⁷ Oxidation of **73** with hydrogen peroxide was accompanied by partial dehydrogenation yielding 1,2,3,4-tetrahydrodibenzothiophene 5,5-dioxide (**68**).²⁵²



Ozonolysis of 1,2,3,4,4a,5a,6,7,8,9-decahydrodibenzothiophene 5,5-dioxide (**76**) yields the ozonide (**77**).³⁴⁹ It has been recorded that addition of bromine to **76** followed by a double dehydrobromination yields an octahydrodibenzothiophene sulfone of unknown structure.³⁵⁰ NMR should establish if it is the sulfone of the known octahydro compound (**73**) or one of the two possible isomers. An octahydrodibenzothiophene



dioxide has been patented as an oil additive but no details of its structure were given.²⁵⁵

The synthesis of several substituted octahydrodibenzothiophenes is described in Sections IV,C and VI,A,3.

VI. Derivatives of Dibenzothiophene

A. ALKYL DERIVATIVES

1. Monomethyl Derivatives

At the time of the previous review¹ only 4-methyldibenzothiophene was known. Since then various syntheses of the four monomethyldibenzothiophenes have been reported along with five dimethyl compounds, two trimethyl compounds, and eight tetramethyl compounds.

³⁴⁹ R. Criegee, *Ann. Chem.* **583**, 6 (1953).

³⁵⁰ H. J. Backer, J. Strating, and L. H. H. Huisman, *Rec. Trav. Chim. Pays-Bas* **60**, 381 (1941).

The mono- and dimethyl compounds were synthesized for exploratory reasons while the tri- and tetramethyl compounds were in general synthesized to confirm the structure of naturally occurring alkyldibenzothiophenes. All of these compounds are listed in Table II. As would be expected, the melting points of many of the isomers are close; thus the melting point of at least one derivative is given, although usually more than one derivative is recorded in the original text.

a. *1-Methyldibenzothiophene*. Reductive silylation of 1-dibenzothiophenecarboxylic acid yields the 1-methyl compound (70%).³¹¹ This reduction coupled with the ready synthesis of the 1-acid (Section VI, G, 1) makes this the best route to 1-methyldibenzothiophene (35% from 2-allylbenzo[*b*]thiophene). It has also been synthesized from the less readily available 1-bromodibenzothiophene (43%)³⁵¹ and as a separable mixture with 3-methyldibenzothiophene via the 2-chlorocyclohexanone route^{302, 305} (Section IV, A).

b. *2-Methyldibenzothiophene*. 2-Methyldibenzothiophene is readily available from 2-bromodibenzothiophene via lithium exchange and treatment with dimethyl sulfate. Conducting the reaction at 0° gives a 92% yield,⁸⁵ while at room temperature this is reduced to 35%.³⁵¹ This material is also formed in good yield by the 2-chlorocyclohexanone route (Section IV, A) (40%).^{302, 305} Alternatively it has been isolated from Pschorr cyclization of 4-methyl-2'-aminodiphenyl sulfide (30%)³⁵² or from 4-methyl-2'-bromodiphenyl sulfide via Grignard formation and treatment with cobalt chloride (5%).³²³ A compound thought to be 2-methyldibenzothiophene has been isolated from the heavy fractions of Lacq petroleum.¹³ Bromination of 2-methyldibenzothiophene gave a mixture from which 3-bromo-2-methyldibenzothiophene was obtained by crystallization (18%).⁸⁵

c. *3-Methyldibenzothiophene*. 3-Methyldibenzothiophene is slightly less accessible than the other three isomers. It can be isolated by treatment of 3-lithiodibenzothiophene with dimethyl sulfate (45%)³⁵¹ or by Huang-Minlon reduction of 3-dibenzothiophenecarboxaldehyde (88%).⁸⁵ However, both of these methods depend on the relatively inaccessible 3-bromodibenzothiophene. It has been reported to be formed via the 2-chlorocyclohexanone route (Section IV, A) in 48% yield as an oil,³⁰⁵ however, this sequence has also been reported to yield a separable mixture of 1-methyl- and 3-methyldibenzothiophene.³⁰² It is probably best prepared by decarboxylation of 3-methyl-1-dibenzothiophenecarboxylic acid³¹¹ (Section IV, B, 1).

³⁵¹ H. Gilman and G. R. Wilder, *J. Org. Chem.* **22**, 523 (1957).

³⁵² M. Kuroki, *Nippon Kagaku Zasshi* **89**, 527 (1968).

TABLE II: METHYL-SUBSTITUTED DIBENZOTHIOPHENES

Substituents	Melting point (°C)	Ref.	Derivatives	Melting point (°C)	Ref.
1-Me	71	311	Sulfone	191-192	351
	67-68	302, 351			
2-Me	77-80	85	Sulfone	197-199	351
	85	13, 302, 305, 323, 352	Picrate	117-118	305, 352
	88-89	351			
3-Me	77-79	85, 302, 305, 311, 351	Sulfone	184-185	351
			Picrate	88-89	305
4-Me	66-67	89, 305	Sulfone	178-179	89
	(98) ^a	76		204-205	351
	(74-75) ^a	2, 11, 12	Picrate	110-111	89
2,8-Me ₂	119-121	85	Sulfone	297-298	311, 325
	122-123	76, 325, 351		290-292	351
3,7-Me ₂	151-152	76, 325	Sulfone	222-223	76
4,6-Me ₂	154-155	2, 3, 11, 12, 14, 23, 76	Sulfone	294	14, 76, 23
			Picrate	130-131	14, 23
3,4-Me ₂	71-72	89	—	—	—
1,4-Me ₂	b.p. 139°/0.07	91	—	—	—
2,4,8-Me ₃	72-73	17	Trinitrobenzoate	166	17
2,6,7-Me ₃	125-126	17	Sulfone	188-290	17
1,2,6,7-Me ₄	127-128	15	Trinitrobenzoate	176-178	15
1,3,7,9-Me ₄	109	95, 316	Picrate	115	95, 316
2,3,6,7-Me ₄	192-194	15	Sulfone	308-309	15
			Trinitrobenzoate	184-185	15
2,3,7,8-Me ₄	211-212	15	Sulfone	339-340	15
2,4,6,7-Me ₄	142-143	17	Trinitrobenzoate	179-182	17
2,4,6,8-Me ₄	142-143	15	Sulfone	304-305	356
	121-122	356			
2,3,6,8-Me ₄	132-134	15	Sulfone	272-275	15
3,4,6,7-Me ₄	196	15, 17	Sulfone	235-237 (d)	17

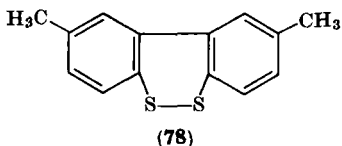
^a See text.

d. *4-Methyldibenzothiophene*. The original method of preparation of this isomer was by treatment of 4-lithiodibenzothiophene with dimethyl sulfate.¹ The purity of the product prepared by this route has since been disputed⁸⁹ and it is probably best prepared by the 2-chlorocyclohexanone route (Section IV,A) (71%). Some confusion appears in the literature over the melting point of 4-methyldibenzothiophene. Synthetic material has a melting point of 66°–67°,^{1, 89, 305} while material isolated from crude oil^{2, 11, 12} is reported to have a melting point of 74°–75° and that obtained as a by-product of the preparation of 4,6-dimethyldibenzothiophene is reported to melt at 98°. ⁷⁶ The latter material could well be dibenzothiophene (m.p. 98°) and the natural material one of the isomeric compounds or a mixture of isomers (2-methyldibenzothiophene occurs in oil¹³). 4-Methyldibenzothiophene is reported to be resistant to desulfurization with Raney nickel, which has been attributed to steric factors.¹⁴ The electrophilic substitution of 4-methyldibenzothiophene has been studied in detail.⁸⁹ Succinylation (Section VI,G,2), acetylation (Section VI,F,2), and nitration (Section VI,E,1) occur in the 2-position while bromination occurs mainly in the 3-position (30%) and in the 2-position (3%). Taking into account the yields obtained it would appear that electrophilic substitution occurs in both the 2- and 3-positions, the isomer actually isolated depending upon the relative solubilities in the crystallization solvent employed. Nitration of 4-methyldibenzothiophene 5,5-dioxide occurs in the 3-position (17%)⁸⁹ (Section VI,E,1). This change in the position of nitration upon oxidation of the sulfur atom parallels the behavior of dibenzothiophene,¹ although the low yield precludes any firm conclusions from being reached.

2. *Dimethyl Derivatives*

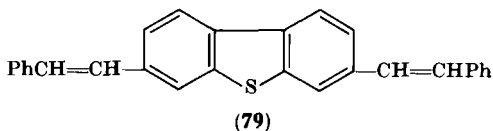
4,6-Dimethyldibenzothiophene has been isolated from several crude oils^{2, 3, 11–14, 23} and has been synthesized from 3,3'-dimethyl-2,2'-dihydroxydiphenyl with phosphorus pentasulfide.²³ Treatment of dibenzothiophene with excess butyllithium followed by methylation yields the 4,6-dimethyl compound (15%)⁷⁶ along with material said to be 4-methyldibenzothiophene. Both compounds are resistant to attack by Raney nickel.¹⁴ 2,8-Dimethyldibenzothiophene is best prepared via lithium exchange with 2,8-dibromodibenzothiophene (improved preparation, Section VI,C,3) and treatment with dimethyl sulfate. When conducted at 0° a 52% yield is obtained,⁷⁶ but at room temperature this is reduced to 32%.³⁵¹ It has also been formed via Huang–Minlon reduction of 2,8-dibenzothiophenedicarboxaldehyde (84%).⁸⁵ A novel route to the 2,8-dimethyl compound has been described involving pyrolysis of 2,9-dimethyldibenzo[*c,e*]-*o*-dithiin (78), or its 5,5-dioxide,

with copper bronze (80%).³²⁵ The starting material is prepared by reduction of 5,5'-dimethyldiphenyl-2,2'-disulfonyl dichloride with hydrogen iodide in acetic acid. By the same route 3,7-dimethyldibenzothiophene has been prepared (92%)³²⁵ from the appropriately substituted disulfonyl dichloride. It is also formed from 3,7-dibromodibenzothiophene via lithiation and methylation (60%).⁷⁶ 1,9-Dimethyldibenzothiophene has not been reported but could be prepared via deamination of



3,7-diamino-1,9-dimethyldibenzothiophene³⁵³ (Section VI, E, 2) or by a modification of the synthesis of 1,3,7,9-tetramethyldibenzothiophene from thiophene [Section IV, C; Eq. (2)]. 3,4-Dimethyldibenzothiophene has been prepared by reduction of 4-methyl-3-dibenzothiophene-carboxaldehyde (66%)⁸⁹ and 1,4-dimethyldibenzothiophene via the 2-chlorocyclohexanone route⁹¹ (Section IV, A). The 1,4-dimethyl compound has been used several times recently as an intermediate in the synthesis of sulfur analogs of the indole alkaloid ellipticine (Section VI, F, 1) and could perhaps be better prepared from 1,4-dibromodibenzothiophene (Section VI, C, 3) via dilithiation and methylation.

Both 2,8-dimethyl- and 3,7-dimethyldibenzothiophene have been reacted with a variety of aromatic aldehydes in DMF yielding distyryl compounds of type 79.³⁵⁴ Yields were best for 3,7-dimethyldibenzothiophene and in the case of its condensation with 3-pyridinecarboxaldehyde the product was of value as a synthetic fiber fluorescent agent.³⁵⁵



3. Tri- and Tetramethyl Derivatives

Eight tetramethyl compounds have been characterized, most having been isolated from natural sources and independently synthesized by

³⁵³ W. Theilacker and F. Baxmann, *Ann. Chem.* **581**, 117 (1953).

³⁵⁴ A. E. Siegrist and H. R. Meyer, *Helv. Chim. Acta* **52**, 1282 (1969).

³⁵⁵ A. E. Siegrist and H. R. Meyer, German Patent 1,965,654 (1970); *Chem. Abstr.* **73**, 110910 (1970).

Carruthers and Douglas.¹⁵⁻¹⁷ The method of synthesis was via Pschorr cyclization of the appropriately substituted *o*-aminodiphenyl sulfide; yields varied from 1 to 10% and the structures of all the products were unequivocal. Armarego and Turner have synthesized 2,4,6,8-tetramethyldibenzothiophene by a different route,³⁵⁶ again unequivocally; however, their recorded melting point is 20° lower than Carruthers and Douglas report.¹⁵ The higher melting sample was chromatographically pure and must be taken as correct. Carruthers and Douglas employ an alternative numbering system for dibenzothiophene but in this text and in Table II conversion to the normal system has been made. An alternative synthetic route to polymethyldibenzothiophenes is illustrated by the synthesis of 1,3,7,9-tetramethyldibenzothiophene (Section IV, C).

The synthesis of octamethyldibenzothiophene from the tetramethyl compound (61) should be possible (Section V, A).

4. Cyclohexyl Derivatives

Several cyclohexyl derivatives of dibenzothiophene have been prepared by the general technique of treating the appropriate bromodibenzothiophene with magnesium and cyclohexanone, followed by reduction of the resultant cyclohexenyl derivative with hydrogen and palladium on charcoal.³⁵⁷ Using this method the following compounds have been prepared: 1-cyclohexyl- (82%), 2-cyclohexyl- (58%), 3-cyclohexyldibenzothiophene (56%), 2,8-dicyclohexyl- (42%), and 1,4-dicyclohexyldibenzothiophene (56%). Treatment of dibenzothiophene with cyclohexene under Friedel-Crafts conditions³⁵⁸ gave one fraction (30%) containing mainly 2- and 3-cyclohexyldibenzothiophene and another (15%) containing mainly dicyclohexyl compounds.

5. S-Alkylthiophenium Salts

Treatment of dibenzothiophene with alkyl halides in the presence of silver tetrafluoroborate or triaryloxonium tetrafluoroborate has recently been shown to yield the corresponding 5-alkyl salts of type 80.^{96, 359} Compounds thus prepared include 5-methyl- (93%), 5-ethyl- (98%), and 5-isopropyldibenzothiophenium tetrafluoroborate (14%). The products were thermally unstable, reverting to dibenzothiophene, although the corresponding perchlorates were more stable. 5-Methoxy-

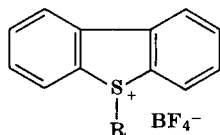
³⁵⁶ W. L. F. Armarego and E. E. Turner, *J. Chem. Soc.*, 13 (1957).

³⁵⁷ Monsanto Chemicals Ltd., French Addition 80,790 (1963); *Chem. Abstr.* **60**, 1704 (1964).

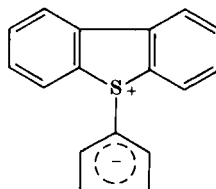
³⁵⁸ Monsanto Chemicals Ltd., French Addition 81,331 (1963); *Chem. Abstr.* **60**, 4113 (1964).

³⁵⁹ R. M. Acheson and D. R. Harrison, *Chem. Commun.*, 724 (1969).

dibenzothiophenium perchlorate (Section VI,D), upon treatment with sodium cyclopentadienide yields the thermally stable zwitterionic cyclopentadienide (**81**) (28% overall).³⁶⁰



(80)



(81)

B. ARYL DERIVATIVES

1. Monoaryl Derivatives

Prior to 1962 no phenyl derivatives of dibenzothiophene were known. The four possible monophenyl derivatives have now been prepared by the general route of treating the appropriate bromodibenzothiophene with magnesium and reacting the derived Grignard with cyclohexanone. Dehydrogenation of the derived cyclohexenyl derivatives with either selenium or palladium on carbon at 300° affords the four monophenyl-dibenzothiophenes in yields varying from 11 to 34%.^{146, 357} The material isolated by Graebe³⁶¹ during his work on the synthesis of dibenzothiophene from diphenyl sulfide, which analyzed for a monophenyldibenzothiophene, has a different melting point from any of the monophenyl derivatives described above, and its structure is still unknown.

As planar projection diagrams³⁶² indicate, considerable overcrowding occurs in 1-phenyldibenzothiophene between the hydrogen atoms on the phenyl substituent and the adjacent C-9 proton.¹⁴⁶ To a lesser extent this is also true of the 4-phenyl derivative due to partial overlap of the phenyl substituent with the sulfur atom of the thiophene ring. A detailed study¹⁴⁶ of the UV spectra of the four monophenyl derivatives and the association constants of their 2,4,7-trinitrofluorenone complexes reveals that both 1-phenyl- and 4-phenyldibenzothiophene have the phenyl substituent orthogonal to the plane of the heterocycle, while both 2-phenyl- and 3-phenyldibenzothiophene are essentially planar.

³⁶⁰ R. M. Acheson and J. K. Stubbs, *J. Chem. Soc., Perkin Trans. I*, 899 (1972).

³⁶¹ C. Graebe, *Ann. Chem.* **174**, 177 (1874).

³⁶² E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

Two of the available theoretical discussions on the positional reactivity of dibenzothiophene^{69,71} have predicted superior reactivity for the 1- and 4-positions in radical reactions. Supporting this, it has now been reported that free-radical phenylation of dibenzothiophene using either benzoyl peroxide³⁶³ or benzenesulfonyl chloride³⁶⁴ gives substitution at all four positions, with preference for the 1- and 4-positions. Arylation using benzenesulfonyl chloride at 250°–270°^{365–367} gives a 40% yield of monophenyl derivatives which contains 1-phenyl- (32%), 2-phenyl- (13%), 3-phenyl- (21%), and 4-phenyldibenzothiophene (33%). The addition of cuprous chloride and raising the reaction temperature to ~400° is stated to give a similar isomer distribution.³⁶⁸ Chlorobenzene and phenylsulfonyldibenzothiophenes are also formed, as by-products, by a radical mechanism.³⁶⁵ Arylation using benzoyl peroxide at 110° gives a solid (20%) of similar composition to the above.^{365,369}

4,4'-Bis(dibenzothiophene) is formed upon heating 4-iododibenzothiophene in the presence of copper bronze at 260° (30%).³⁵¹

Aryl derivatives of dibenzothiophene are generally described as being thermally stable up to 400° and are therefore of use as heat-transfer media, dielectric or hydraulic fluids, lubricants, and stationary phases for vapor-phase chromatography.^{369–372} 3-Phenyldibenzothiophene 5,5-dioxide is capable of detecting X, γ , or corpuscular radiation when incorporated in photographic film.¹⁶⁸

2. Di- and Tetraaryl Derivatives

Treatment of the benzo[*b*]thiophene derivative (82) with perchloric acid yields 2,4-diphenyldibenzothiophene.²⁶⁴ Reaction of 2,3-dibromo-

³⁶³ A. L. J. Beckwith and M. J. Thompson, *J. Chem. Soc.* 73 (1961).

³⁶⁴ P. J. Bain, E. J. Blackman, W. Cummings, S. A. Hughes, E. R. Lynch, E. B. McCall, and R. J. Roberts, *Proc. Chem. Soc.*, 186 (1962).

³⁶⁵ E. B. McCall, A. J. Neale, and T. J. Rawlings, *J. Chem. Soc.*, 5288 (1962).

³⁶⁶ E. B. McCall and R. J. Roberts, British Patent 919,088 (1963); *Chem. Abstr.* 59, 1601 (1963).

³⁶⁷ E. B. McCall and R. J. Roberts, British Patent 928,320 (1963); *Chem. Abstr.* 59, 12763 (1963).

³⁶⁸ E. B. McCall and W. Cummings, British Patent 970,911 (1964); *Chem. Abstr.* 61, 14580 (1964).

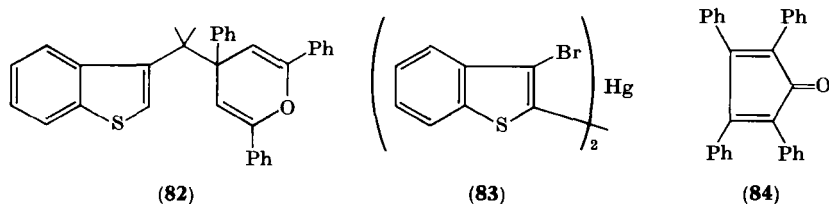
³⁶⁹ E. B. McCall and T. J. Rawlings, British Patent 995,155 (1965); *Chem. Abstr.* 63, 13215 (1965).

³⁷⁰ Monsanto Chemicals Ltd., French Patent 1,351,472 (1964); *Chem. Abstr.* 61, 9468 (1964).

³⁷¹ E. B. McCall and P. J. Bain, British Patent 1,000,964 (1965); *Chem. Abstr.* 63, 14817 (1965).

³⁷² E. B. McCall and T. J. Rawlings, British Patent 932,813 (1963); *Chem. Abstr.* 60, 504 (1964).

benzo[*b*]thiophene with butyllithium and mercuric chloride yields the mercury compound (83),³⁷³ which on thermolysis in the presence of 2,3,4,5-tetraphenyl-2,4-cyclopentadienone (84) (tetracyclone) yields



1,2,3,4-tetraphenyldibenzothiophene (54%).¹⁵³ Thermolysis of 3-bromobenzo[*b*]thiophene in tetracyclone gave the same compound (76%).

3. Benzyl Derivatives

No pure benzyldibenzothiophenes have been prepared; however, the reaction of dibenzothiophene with benzyl chloride is reported to yield a mixture of the four monobenzyldibenzothiophenes in equal proportions (combined yield 21%).^{370, 371} The addition of aluminum chloride to the reaction mixture substantially increased the proportion of the 4-derivative. Reaction of the appropriate lithiodibenzothiophene with benzyl chloride should give the pure isomers.

C. HALOGEN DERIVATIVES

1. Fluorodibenzothiophenes

No monofluoro derivatives of dibenzothiophene have been reported. However, they should be readily available from the appropriate amino-dibenzothiophene via the Sandmeyer reaction or by treatment of the required lithiodibenzothiophene with FCIO_3 , as has been used for related systems.³⁷⁴

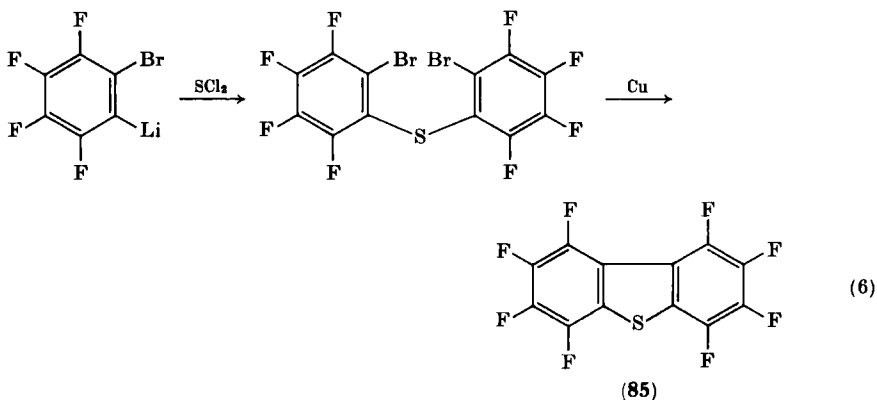
The formation and properties of octafluorodibenzothiophene (85) have been the subject of a series of papers by Chambers *et al.* Ullman coupling of bis(2-bromotetrafluorophenyl)sulfide gives 85 in quantitative yield^{227, 375} [Eq. (6)]. An alternative route to 85 involves treating 2,2'-dihydrooctafluorobiphenyl with butyllithium and reacting the

³⁷³ W. Ried and H. Bender, *Chem. Ber.* **88**, 34 (1955); **89**, 1574 (1956).

³⁷⁴ R. D. Schuetz, D. D. Taft, J. P. O'Brien, J. L. Shea, and H. M. Mork, *J. Org. Chem.* **28**, 1420 (1963).

³⁷⁵ R. D. Chambers, J. A. Cunningham, and D. A. Pyke, *Tetrahedron* **24**, 2783 (1968).

derived dilithio derivative (**86**) with sulfur dichloride (66%).³⁷⁶ Finally, reaction of tetrafluorobenzynes with the anion of pentafluorothiophenol



affords **85** in good yield.³⁷⁷ The octafluoro compound (**85**) was smoothly desulfurized with Raney nickel to give 2,2'-dihydrooctafluorobiphenyl^{110, 378} and was recovered after heating for 4 days at 420° in the presence of copper.³⁷⁸ Oxidation of **85** with the usual reagents proved difficult; however, 85% hydrogen peroxide in trifluoroacetic anhydride smoothly converted it to the corresponding sulfone.^{110, 379} Pyrolysis of octafluorodibenzothiophene 5,5-dioxide gave octafluorodibenzofuran (72%), a novel compound. A similar conversion, involving loss of SO, was observed in the mass spectrum of this sulfone (Section III, B, 2).^{110, 379}

Reaction of **85** with sodium methoxide in methanol gave the 3-methoxy derivative (**87**) (83%) together with a small amount of the corresponding 3,7-dimethoxy derivative.⁸¹ Earlier publications of this work had erroneously described these derivatives as being heptafluoro-2-methoxy and hexafluoro-2,8-dimethoxydibenzothiophene, respectively,^{110, 376, 378} the correct structures being finally arrived at by consideration of their ¹H and ¹⁹F NMR spectra. The change in assignment of structure was supported by a direct synthesis of heptafluoro-2-methoxydibenzothiophene from tetrafluorobenzynes and 2,3,5,6-tetrafluoro-4-methoxythiophenol and establishment that it was different from **87**.⁸¹ Hexafluoro-

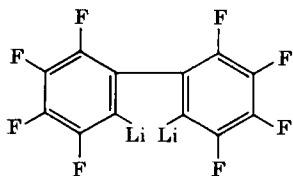
³⁷⁶ R. D. Chambers, J. A. Cunningham, and D. J. Spring, *Tetrahedron* **24**, 3997 (1968).

³⁷⁷ R. D. Chambers and D. J. Spring, *Tetrahedron Lett.*, 2481 (1969).

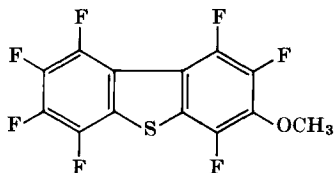
³⁷⁸ R. D. Chambers and J. A. Cunningham, British Patent 1,180,743 (1970); *Chem. Abstr.* **72**, 132501 (1970).

³⁷⁹ R. D. Chambers and J. A. Cunningham, *Chem. Commun.*, 583 (1967).

3,7-dimethoxydibenzothiophene was also synthesized from both hexafluoro-2,2'-dihydro-4,4'-dimethoxybiphenyl (~50%) and from 2,2'-dibromohexafluoro-4,4'-dimethoxybiphenyl (44%) by the methods described above for **85**.⁸¹ Reaction of **85** with ammonia at 128° afforded an unstable monoamine (56%) of uncertain structure.³⁸⁰



(86)



(87)

Nucleophilic substitution in octafluorodibenzothiophene 5,5-dioxide by methoxide ion occurred in the same position, giving heptafluoro-3-methoxydibenzothiophene 5,5-dioxide, which was prepared independently by oxidation of **87** (89%).⁸¹

2. Chlorodibenzothiophenes

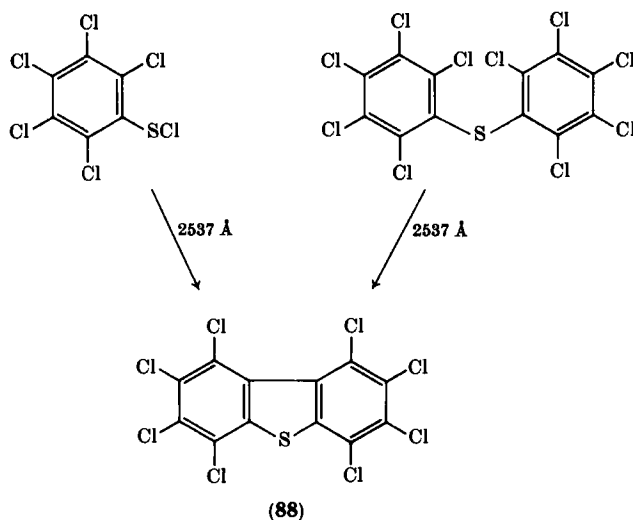
Low-temperature chlorination of dibenzothiophene with elemental chlorine produces a chlorine adduct at the sulfur atom which is readily decomposed to dibenzothiophene 5-oxide.¹ However, nuclear chlorination of dibenzothiophene has still not been studied. 2-Chlorodibenzothiophene has been prepared by the Sandmeyer reaction on 2-amino-dibenzothiophene¹ and this route has now been extended to give 1-chloro-, 3-chloro-, and 4-chlorodibenzothiophene in average yields of 15%.³⁵¹ An alternative route to 1-chlorodibenzothiophene is described in Section VI, E, 1, involving treatment of 1-nitro-2-acetamidodibenzothiophene with ethanolic HCl (34%). Both of these routes are tedious, the second probably less so than the first. 4-Chlorodibenzothiophene has been prepared in good yield via the *o*-chlorocyclohexanone route (Section IV, A) and this is undoubtedly the method of choice. Attempts to prepare the 2-chloro compound by this route gave very low yields.³⁰² According to the older literature the preferred method of preparation of 2-chlorodibenzothiophene was via treatment of 2-nitrodibenzothiophene with thionyl chloride, which was reported to proceed in good yield.³⁸¹

³⁸⁰ Presented with the related material in Chambers and Cunningham.³⁷⁸ The structure of this product was originally given as 2-aminoheptafluorodibenzothiophene but may be revised (private communication from R. D. Chambers).

³⁸¹ C. Courtot, L. Nicolas, and T. H. Liang, *Compt. Rend. Acad. Sci., Ser. C* **186**, 1624 (1928).

An unsuccessful attempt to repeat this reaction was made by Bird;³⁸² however, he was able to show that dibenzothiophene 5-oxide did, in fact, react with either thionyl chloride or phosphorus oxychloride to yield 2-chlorodibenzothiophene in good yield. Since all methods of nitration of dibenzothiophene yield a mixture of 2-nitrodibenzothiophene and dibenzothiophene 5-oxide, which have identical melting points, it was concluded that the earlier workers had in fact been working with the sulfoxide and not the nitro compound. The reaction was rationalized as being a deoxygenative halogenation of a heterocyclic *S*-oxide akin to the Meisenheimer reaction of *N*-oxides,³⁸³ which already had precedents in the sulfoxide field.³⁸⁴ Unfortunately the 2-chlorodibenzothiophene prepared by this route is contaminated with 2,8-dichlorodibenzothiophene which cannot be removed by crystallization. The best method of preparation of this compound is therefore via a Sandmeyer reaction on 2-aminodibenzothiophene.¹

Octachlorodibenzothiophene (**88**) has been formed¹¹¹ by irradiation of a solution of pentachlorobenzenesulfonyl chloride in CCl_4 in a low-pressure, cold cathode mercury arc (62%). A similar photolysis of bis(pentachlorophenyl) sulfide, prepared by the action of sulfur monochloride and sulfuryl chloride on benzene in the presence of aluminum chloride, also yielded **88** (42%). Both routes are shown in Scheme 4.



SCHEME 4

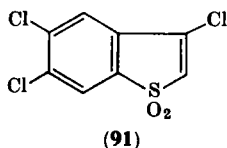
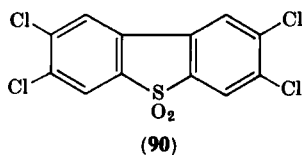
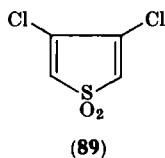
³⁸² C. W. Bird, *J. Chem. Soc. C*, 1230 (1968).

³⁸³ E. Ochial, "Aromatic Amine Oxides," p. 259. Elsevier, Amsterdam, 1967.

³⁸⁴ F. Loth and A. Michaelis, *Chem. Ber.* **27**, 540 (1894).

A more practical synthesis of **88** has been described involving chlorination and ring closure of bis(*p*-chlorophenyl) sulfide with a mixture of chlorine, sulfur, and aluminum chloride at 60° (82%).³⁸⁵ The octachloro compound (**88**) is reported to be very stable, showing little fragmentation in the mass spectrometer,¹¹¹ and to be useful as a plasticizer, flame-proofing agent, antioxidant, and vulcanization accelerator.³⁸⁵

The self-condensation of 3,4-dichlorothiophene 1,1-dioxide (**89**) in refluxing xylene yields trace amounts of 2,3,7,8-tetrachlorodibenzothiophene 5,5-dioxide (**90**). The major product (50%) is the benzothiophene (**91**) formed by loss of SO₂ and HCl from the Diels–Alder dimer of **89**. Further treatment of **91** with **89** in refluxing trichlorobenzene again yields **90** (23%).³⁸⁶ Compound **90** is reported to possess insecticidal properties.³⁸⁷



Chlorination of 2-acetamidodibenzothiophene with sulfonyl chloride has been shown to occur in the 1-position³⁸⁸ by deamination of the product and comparison with the known 1-chlorodibenzothiophene,³⁸⁹ rather than in the 3-position, as was originally believed.³⁹⁰ In contrast, chlorination of 2-benzamidodibenzothiophene has been shown to occur in the 3-position.³⁸⁸ A similar change in the position of further substitution when passing from 2-acetamido- to 2-benzoamidodibenzothiophene was observed upon nitration (Section VI,E,1). Chlorination of both 3-acetamido- and 3-benzamidodibenzothiophene yielded a mixture of

³⁸⁵ H. Klug, German Patent 1,222,508 (1966); *Chem. Abstr.* **65**, 13727 (1966).

³⁸⁶ H. Bluestone, R. N. Bimber, R. Berkey, and Z. Mandel, *J. Org. Chem.* **26**, 346 (1961).

³⁸⁷ R. M. Bimber and H. Bluestone, U.S. Patent 3,136,782 (1964); *Chem. Abstr.* **61**, 5612 (1964).

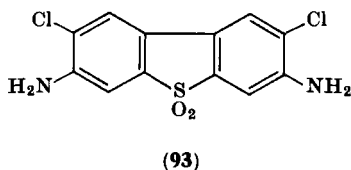
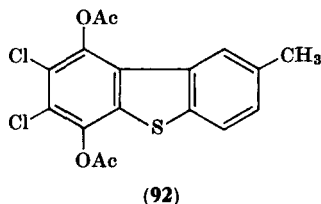
³⁸⁸ H. Gilman and G. R. Wilder, *J. Amer. Chem. Soc.* **77**, 6059 (1955).

³⁸⁹ H. Gilman and G. R. Wilder, *J. Amer. Chem. Soc.* **76**, 2906 (1954).

³⁹⁰ H. Gilman and S. Avakian, *J. Amer. Chem. Soc.* **68**, 1514 (1946).

the 2-chloro isomer and another, assumed to be the 4-chloro isomer. Both of the 2-chloroamides were hydrolyzed to the same amine, which upon deamination and oxidation yielded the known 2-chlorodibenzothiophene 5,5-dioxide.³⁸⁸

The dichloro compound (92) was isolated after treatment of chlorinated *p*-benzoquinone with *p*-toluenesulfonylhydrazine in acetic anhydride.³⁹¹ Treatment of 3,3'-dichloro-4,4'-diaminobiphenyl with oleum yields the 2,8-dichlorodibenzothiophene (93).³⁹²



3. Bromodibenzothiophenes

The synthesis of 4-bromodibenzothiophene³⁹³ completes the series of the four monobromodibenzothiophenes. However, the synthesis of the 1-bromo and the 3-bromo compounds is somewhat long, and several routes can be devised, each with differing merits. In view of the great synthetic value of the derived lithio derivatives, available routes to each of the monobromodibenzothiophenes are discussed below, overall yields being based on dibenzothiophene as starting material in each case.

a. *1-Bromodibenzothiophene*. Two routes exist for the preparation of this compound, each dependent on the ability of the acetamido group when present in position 2 or 4 of dibenzothiophene, to direct further substitution to the 1-position. The highest yield route consists of treating 4-lithiodibenzothiophene with *O*-methylhydroxylamine to give 4-aminodibenzothiophene³⁹⁰ followed by acetylation, bromination in the 1-position, deacetylation, and deamination, yielding 1-bromodibenzothiophene in five steps (24%).³⁹⁴ Alternatively, 2-acetamidodibenzothiophene can be nitrated in the 1-position and the derived nitro amine converted to the 1-bromo compound by treatment with hydrobromic acid in ethanol.³⁸⁹ This route has been made more attractive by the recent high-yield synthesis of 2-acetyldibenzothiophene

³⁹¹ W. Reid and R. Dietrich, *Ann. Chem.* **57**, 649 (1961).

³⁹² H. J. Exner and R. Puettter, German Patent 1,058,173 (1959); *Chem. Abstr.* **58**, 607 (1963).

³⁹³ H. Gilman and D. L. Esmay, *J. Amer. Chem. Soc.* **76**, 5786 (1954).

³⁹⁴ H. Gilman and A. L. Jacoby, *J. Org. Chem.* **3**, 108 (1938).

from the 2-lithio compound.⁸⁵ Beckmann rearrangement of the derived oxime yields the 2-acetamido compound in good yield.³⁹⁴ Combining all of these steps gives a 14% overall yield of the 1-bromo compound.

b. *2-Bromodibenzothiophene*. Bromination of dibenzothiophene in carbon disulfide readily affords the 2-bromo compound.²⁴⁹ The material thus obtained, after one recrystallization from ethanol, has a melting point of $\sim 115^\circ$. Considerable losses occur in raising the melting point to the quoted 126° – 127° and for general synthetic purposes the lower melting material is adequate.^{94, 146} The use of methylene chloride as solvent has recently been shown to yield the 2-bromo compound contaminated with both starting material (10%) and 2,8-dibromodibenzothiophene (10%).⁹⁶ Oxidation of the 2-bromo compound to 2-bromodibenzothiophene 5,5-dioxide with hydrogen peroxide has been recorded using a modified procedure which could be of general value.²³⁵

c. *3-Bromodibenzothiophene*. The usual route to this isomer is via nitration of dibenzothiophene 5-oxide in the 3-position, followed by reduction with stannous chloride to 3-aminodibenzothiophene.³⁹⁵ The Sandmeyer reaction with cuprous bromide in HBr yields the 3-bromo compound³⁹⁶ (13% overall). Disadvantages of this route are that the Sandmeyer reaction has been optimized at 23% and difficulties have been experienced in repeating the reductive step, a slightly modified procedure being described giving lower, but reproducible yields.⁸⁵ An alternative route to 3-bromodibenzothiophene could be employed involving nitration of dibenzothiophene 5,5-dioxide in the 3-position followed by reduction of the nitro group and conversion to 3-bromodibenzothiophene 5,5-dioxide via the Sandmeyer reaction.³⁹⁷ Reduction of the sulfone moiety with LAH²³⁵ yields the 3-bromo compound (10% overall). The same reduction with LAH under slightly different conditions has been reported to yield dibenzothiophene.⁸⁵ Reductive debromination has been known to occur with LAH; however, the small amount of dibenzothiophene actually isolated, coupled with the fact that dibenzothiophene and 3-bromodibenzothiophene have almost identical melting points casts doubts upon the validity of this result; moreover, 3,7-dibromodibenzothiophene 5,5-dioxide does not suffer debromination during LAH reduction of the sulfone group.⁷⁶ Phenylcalcium iodide metallates dibenzothiophene in the 3-position; attempts to treat this with bromine to give 3-bromodibenzothiophene were unsuccessful.³⁹³

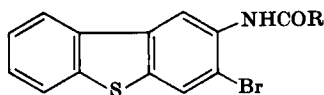
³⁹⁵ R. K. Brown, R. G. Christiansen, and R. B. Sandin, *J. Amer. Chem. Soc.* **70**, 1748 (1948).

³⁹⁶ G. Illuminati, J. Nobis, and H. Gilman, *J. Amer. Chem. Soc.* **73**, 5887 (1951).

³⁹⁷ H. Gilman, A. L. Jacoby, and H. A. Pacevitz, *J. Org. Chem.* **3**, 120 (1938).

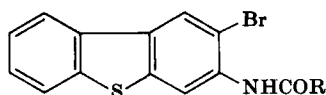
d. *4-Bromodibenzothiophene*. Treatment of 4-lithiodibenzothiophene with bromine yields the 4-bromo compound.^{393, 394}

e. *Miscellaneous Bromodibenzothiophenes*. The preparation of 2,8-dibromodibenzothiophene requires prolonged reflux of dibenzothiophene with bromine in carbon disulfide.²⁴⁹ By substantially reducing the volume of solvent a more vigorous reaction ensues which yields the 2,8-dibromo compound after 1 hour in good yield.⁸⁵ The 2,8-dibromo compound has been obtained from the bromination of 5-methyldibenzothiophenium tetrafluoroborate (76%),⁹⁶ under conditions in which dibenzothiophene gave 2-bromodibenzothiophene. 3,7-Dibromodibenzothiophene has been prepared via reduction of the corresponding sulfone²⁴⁹ with LAH.⁷⁶ The synthesis of 1,4-dibromodibenzothiophene via a Sandmeyer reaction on 1-bromo-4-aminodibenzothiophene has been described,³⁵⁷ however, very few details were recorded. The bromination of 4-methyl- and 2-methyldibenzothiophene is discussed in Section VI, A, 1. Bromination of 4-methoxydibenzothiophene occurs in the 1-position,⁹⁰ the structure of the product being determined by analysis of the NMR spectrum of the derived aldehyde. Bromination of 2-acetamidodibenzothiophene yields the 3-bromo compound (**94a**).³⁹⁰ 2-Benzamidodibenzothiophene yields **94b**.³⁸⁸ The structure of both compounds was established by hydrolysis to the same amine, which in one case was followed by deamination to 3-



(**94a**) R = CH₃

(**94b**) R = Ph



(**95a**) R = CH₃

(**95b**) R = Ph

bromodibenzothiophene. The direction of bromination to the 3-position by a 2-acylamino group parallels the effect of the methyl group of 2-methyldibenzothiophene during bromination⁸⁵ and is one of only a few self-consistent further substitution patterns observed for derivatives of dibenzothiophene (see Section III, C, 2). Bromination of 3-acetamido- and 3-benzamidodibenzothiophene occurs in the 2-position, yielding **95a** and **95b**, respectively, from which 2-bromo-3-aminodibenzothiophene can be obtained by hydrolysis.³⁸⁸

f. *Properties of Bromodibenzothiophenes*. The ready conversion of bromo- and dibromodibenzothiophenes to the corresponding lithio compounds is dealt with in Section VI, H, 1. The use of these lithio derivatives has enabled the synthesis of the corresponding aldehydes, methyl ketones, acids, phenols, trialkylsilyl, tritio, alkyl, and amino compounds to be achieved in high yield (see appropriate sections). The known bromodibenzothiophenes are listed in Table III. The last two

TABLE III
BROMODIBENZOTHIOPHENES

Substituents	Melting point (°C)	Yield (%) from dibenzothiophene	References ^a
1-Br	84	24	^c
2-Br	126–127	79	249
3-Br	97–98	13	^c
4-Br	75–79	21	393 (394)
1,4-Br ₂	—	—	357
2,8-Br ₂	225–226	67	85 (249)
3,7-Br ₂	180	28	76 (249)
2-CH ₃ , 3-Br	124–125	19	85
4-CH ₃ , 3-Br	134–135.5	21	89
4-CH ₃ , 2-Br	100–101.5	2	89
4-OCH ₃ , 1-Br	112	27	90
2-NHCOCH ₃ , 3-Br	199–200	44 ^b	390
2-NH ₂ , 3-Br	135	40	390
2-NHCOPh, 3-Br	201–202	21	388
3-NHCOCH ₃ , 2-Br	222–223	35	388
3-NH ₂ , 2-Br	132–133	20	388
3-NHCOPh, 2-Br	179–180	25	388
4-NHCOCH ₃ , 1-Br	254	54	394
4-NH ₂ , 1-Br	156	52	394
8-NO ₂ , 2-Br	254–256	20	235
3,7-(NO ₂) ₂ ; 2,8-Br ₂ as sulfoxide	283–292 (crude)	32	393
7-NO ₂ , 2-Br as sulfone	319–321	37	235

^a References in parentheses refer to the preparation of intermediates or to older methods.

^b Assuming that the acetamido compound is prepared via Beckmann rearrangement³⁹⁴ from 2-acetyldibenzothiophene.⁸⁵

^c Yields calculated from several isolated steps, see text.

compounds in Table III have been included because reduction of each to the corresponding amines followed by Sandmeyer conversion to the bromo compounds could yield, after reduction of the sulfone group with LAH, 2,3,7,8-tetrabromodibenzothiophene and 2,7-dibromodibenzothiophene, respectively.

4. Iododibenzothiophenes

The synthesis of the four monoiododibenzothiophenes has now been completed using established methods. 1-Iododibenzothiophene is formed from 1-lithiodibenzothiophene upon treatment with iodine

(27%),³⁵¹ essentially as described for the preparation of the 4-iodo compound.¹ The Sandmeyer reaction had been used to prepare 2-iodo- and 2,8-diiododibenzothiophene¹ and this reaction has now been employed to prepare 3-iododibenzothiophene (13%)³⁵¹ and 3,7-diiododibenzothiophene 5,5-dioxide³⁹⁸ from the appropriate amines.

D. HYDROXY AND ALKOXY DERIVATIVES

1. *Hydroxydibenzothiophenes*

The literature concerning hydroxydibenzothiophenes has not progressed very much over the last 20 years, although the necessary intermediates and methods are now available for the synthesis of these compounds. The isolation of 1-hydroxydibenzothiophene 5,5-dioxide as a metabolite of dibenzothiophene is the only reference to the 1-hydroxy compound²⁵⁹ (Section III,C,3); however, two possible precursors, 1-amino- and 1-bromodibenzothiophene are now available. Several good routes to 2-hydroxydibenzothiophene have been described in an earlier review.¹ 3-Hydroxydibenzothiophene has not been reported, but, as well as the availability of 3-amino- and 3-bromodibenzothiophene, a synthesis of 3-methoxydibenzothiophene has been described³⁰⁶ (see Section IV,A), demethylation of which should lead to the required phenol. 4-Hydroxydibenzothiophene is readily formed from 4-lithiodibenzothiophene, full experimental details for its preparation have recently been recorded.⁹⁰ A procedure for the conversion of dibenzothiophene 5,5-dioxide into 4-hydroxydibenzothiophene 5,5-dioxide involving heating to 240° in the presence of copper sulfate and water vapor has been described.³⁹⁹ Treatment of 2-bromodibenzothiophene with anhydrous potassium phenate and copper bronze at 200° afforded 2-phenoxydibenzothiophene (38%), and the 2,8-diphenoxy compound was prepared in a similar manner.⁴⁰⁰ The use of 2,8-dihydroxydibenzothiophene as an oil additive has been discussed.⁴⁰¹ The low-yield synthesis of a chlorinated 1,4-diacetoxy derivative of dibenzothiophene (92) is described in Section VI,C,2.

³⁹⁸ T. Kawai and T. Veda, *Yakugaku Zasshi* **80**, 1651 (1960).

³⁹⁹ D. Stevens and G. H. Harris, U.S. Patent 2,831,895 (1958); *Chem. Abstr.* **52**, 15581 (1958).

⁴⁰⁰ E. B. McCall and T. J. Rawlings, British Patent 932,813 (1963); *Chem. Abstr.* **60**, 504 (1964).

⁴⁰¹ F. P. Richter and E. W. Fuller, U.S. Patent 2,571,384 (1951); *Chem. Abstr.* **46**, 731 (1952).

2. *Alkoxydibenzothiophenes*

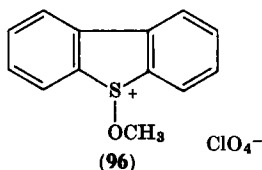
With the exception of 4-methoxydibenzothiophene, which is well characterized, the literature concerning the remaining three monomethoxy compounds is somewhat confused. As mentioned earlier (Section III, C, 3), dibenzothiophene is metabolized as 1-hydroxydibenzothiophene 5,5-dioxide, which was converted to the corresponding methoxy compound by methylation for structure determination.²⁵⁹ The position of the methoxy group was determined by the fact that the melting point of the product was different from those of the other three methoxy sulfones, each of which was listed for the first time, but without details of source or preparation. Tilak had attempted the preparation of 2-methoxydibenzothiophene via the 2-chlorocyclohexanone route (Section IV, A); however, it was unsuccessful.³⁰⁵ The material used in this study was therefore presumably prepared from 2-bromodibenzothiophene via the phenol.^{323, 402} *Chemical Abstracts* does not list 3-methoxydibenzothiophene, although it is included in a table of compounds prepared by Tilak via the 2-chlorocyclohexanone route, without details of structure proof.³⁰⁶ This product could equally well be 1-methoxydibenzothiophene by virtue of its mode of formation (see Section IV, A). The synthesis of 4-methoxydibenzothiophene has been achieved via the 2-chlorocyclohexanone route (11%)³⁰⁵ or more practically via methylation of 4-hydroxydibenzothiophene (38% overall).^{90, 394} The sulfones of the above three methoxy compounds were prepared by peracetic acid oxidation.²⁵⁹ Thus, although the melting points of the four monomethoxydibenzothiophene sulfones have been recorded, only the synthetic details for 4-methoxy- and perhaps 3-methoxydibenzothiophene exist.

Gilman reported, in an early paper, that 4-methoxydibenzothiophene underwent nitration predominantly in the 1-position, with traces of 3-substitution.³⁹⁰ These positions of nitration were not confirmed but were suggested by analogy with the nitration of 4-methoxydibenzofuran. In view of the fact that 4-methyldibenzothiophene is nitrated in the 2-position and brominated predominantly in the 3-position, the nitration of the 4-methoxy compound was repeated.⁹⁰ The structure of the nitration product was confirmed as being 1-nitro-4-methoxydibenzothiophene by reference to the NMR spectra of the product and the starting material. Both NMR and GLC techniques were unable to detect a further isomer. Bromination of the 4-methoxy compound also occurred in the 1-position, as was demonstrated by the NMR spectrum of the derived aldehyde.

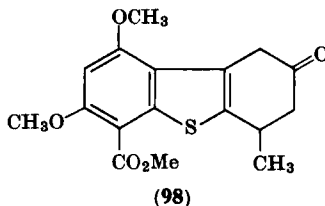
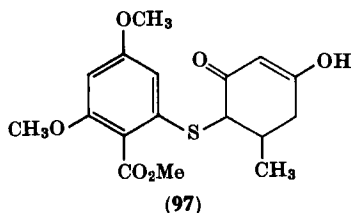
⁴⁰² B. Putzer and F. Muth, German Patent 606,350 (1934); *Chem. Abstr.* **29**, 1434 (1935).

These results would indicate that the product of chlorination of 4-hydroxydibenzothiophene with sulfonyl chloride is, as suggested, 1-chloro-4-methoxydibenzothiophene.¹

Dibenzothiophene 5-oxide is sufficiently nucleophilic to be alkylated at the oxygen atom by alkyl halides in the presence of silver perchlorate (**96**).³⁰⁰ Such compounds were found to be readily hydrolyzed back to the sulfoxide. The reaction of **96** with amines is discussed in Section VI, E, 3.



An attempt to methylate the diketone (**97**) with methanolic hydrogen chloride gave the dimethoxy derivative (**98**), presumably by alkylation of the β -dicarbonyl system by the activated aromatic nucleus.⁴⁰³ The possibility therefore exists of synthesizing polymethoxy derivatives of dibenzothiophene by the 2-chlorocyclohexanone route (Section IV, A), using this modification of the ring-closure step.

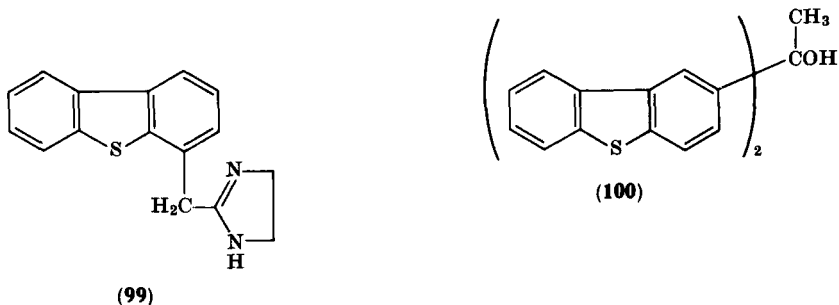


3. Hydroxyalkyl Derivatives

Reduction of ethyl 1-dibenzothiophenecarboxylate with LAH affords 1-hydroxymethyldibenzothiophene (96%), which is smoothly converted into the chloromethyl derivative with thionyl chloride (70%).³¹¹ Both the Cannizzaro reaction and LAH reduction of 2-dibenzothiophenecarboxaldehyde yield the 2-hydroxymethyl derivative in good yields.⁸⁵ 3-Hydroxymethyl-4-methyldibenzothiophene has been prepared via Cannizzaro reaction of the corresponding 3-aldehyde;⁸⁹ however, 3-hydroxymethyldibenzothiophene itself has not been recorded, although the necessary precursors are available. Considerable interest has centered around 4-hydroxymethyldibenzothiophene, which

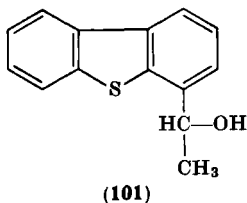
⁴⁰³ H. Newman and R. B. Angier, *J. Org. Chem.* **34**, 3484 (1969).

is formed by reduction of the 4-acid with LAH.^{404, 405} Conversion into the 4-chloromethyl compound followed by treatment with potassium cyanide yields the 4-cyanomethyl compound from which 4-(2-imidazolyl)dibenzothiophene (**99**) is prepared by treatment with ethylenediamine.⁴⁰⁴⁻⁴⁰⁶ Compound **99** is reported to possess cardiotonic, hypotensive, and local anaesthetic properties. Reaction of 2-lithiodibenzothiophene with half an equivalent of ethyl acetate yields the carbinol (**100**) (50%).⁸⁵ 3-Lithio-4-methyldibenzothiophene underwent a similar



reaction (43%),⁸⁹ IR analysis of the progress of each reaction indicating that the corresponding acetyldibenzothiophene was present as an intermediate.

An improved synthesis of 2-(1'-hydroxyethyl)dibenzothiophene has been reported involving Meerwein-Ponndorf reduction of 2-acetyldibenzothiophene.⁴⁰⁷ An alternative synthetic route has been employed in the synthesis of 4-(1'-hydroxyethyl)dibenzothiophene (**101**) involving treatment of 4-lithiodibenzothiophene with acetaldehyde (36%).¹²⁴ Both of these compounds are readily dehydrated to the corresponding vinyl compounds, the polymerization of which is discussed in Section VII.



⁴⁰⁴ K. Pelz, F. Hradil, and M. Protiva, *Collect. Czech. Chem. Commun.* **33**, 1873 (1968); *Chem. Abstr.* **69**, 86737 (1968).

⁴⁰⁵ M. Protiva, K. Pelz, and F. Hradil, Czech. Patent 129,655 (1968); *Chem. Abstr.* **72**, 12727 (1970).

⁴⁰⁶ M. Protiva, K. Pelz, and A. Capek, Czech. Patent 133,122 (1969); *Chem. Abstr.* **73**, 98789 (1970).

⁴⁰⁷ I. V. Andreeva and M. M. Koton, *Zh. Obshch. Khim.* **27**, 997 (1957); *Chem. Abstr.* **52**, 4598 (1958).

E. NITROGEN DERIVATIVES

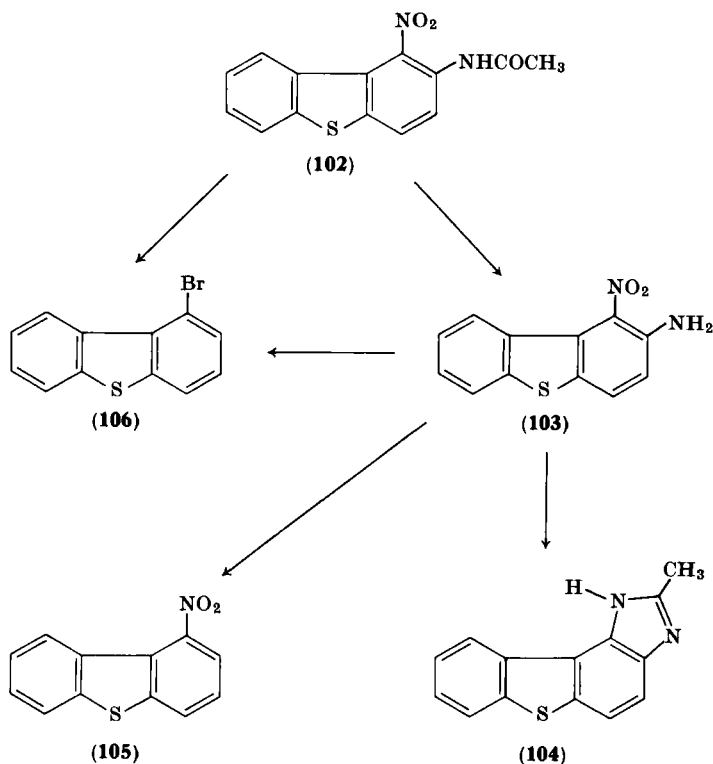
1. Nitrodibenzothiophenes

Direct nitration of dibenzothiophene occurs in the 2-position, while prior oxidation of the sulfur atom to either the sulfoxide or sulfone causes nitration to be directed to the 3-position.¹ These two reactions form the starting point for the synthesis of most of the known derivatives of dibenzothiophene, which normally proceed via the derived amines. This has now been further illustrated by the synthesis of both 1-nitro- and 4-nitrodibenzothiophene from *N*-derivatives of 2- and 3-aminodibenzothiophene, respectively, as described below. The synthesis of these two compounds thus completes the series of mononitrodibenzothiophenes. Unfortunately hopes of synthesizing nitrodibenzothiophenes via the chlorocyclohexanone route have been almost certainly ruled out by the failure to produce 2-nitrodibenzothiophene by this route (Section IV, A).

The nitration of derivatives of 2- and 3-aminodibenzothiophene has been independently studied by Sawicki and Gilman *et al.* This work was carried out between 1953 and 1956, before NMR spectroscopy had become generally available, and consequently chemical and degradative methods had to be employed to establish the structure of new derivatives. However, Sawicki successfully employed ultraviolet spectroscopy to confirm structures by comparing with known π -isoelectronic derivatives of carbazole. Apart from attempting to establish some general rules for the position of further substitution of monosubstituted dibenzothiophenes, the above work made available several new and useful derivatives of dibenzothiophene. The work of Sawicki and Gilman *et al.* is self-consistent where it overlaps and for convenience is not dealt with historically below.

2-Acetamidobenzothiophene is nitrated in the 1-position yielding **102** (73%), which upon hydrolysis with either sodium hydroxide or ethanolic hydriodic acid gives the nitroamine (**103**).³⁸⁹ The same nitroamine was also formed by the nitration and hydrolysis of 2-carbethoxyamino-dibenzothiophene.¹⁵⁴

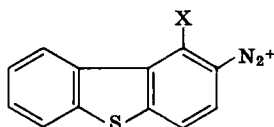
In the latter case the structure was established by reduction with stannous chloride in acetic acid, which afforded the imidazole derivative (**104**), thus proving ortho substitution, followed by comparison of the ultraviolet spectrum of **104** with the two possible benzimidazole derivatives of carbazole. Deamination of **103** via diazotization in sulfuric acid afforded 1-nitrodibenzothiophene (**105**) (54%), being the only recorded route to this compound³⁸⁹ (Scheme 5). Initial attempts to hydrolyze **102** to the nitroamine (**103**) had been made with ethanolic hydrogen chloride



SCHEME 5

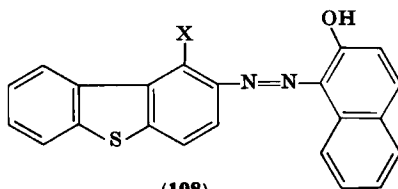
or hydrogen bromide and in each case a nitrogen-free product was obtained.³⁸⁰ The product obtained with hydrogen bromide was shown to be 1-bromodibenzothiophene (**106**) by comparison with an independently synthesized sample (Section VI,C,3). The compound formed with hydrogen chloride was assumed, by analogy, to be 1-chlorodibenzothiophene, and this was later confirmed by independent synthesis from 1-aminodibenzothiophene (Section VI,C,2). The course of both reactions was suggested to be via displacement of the nitro group from the conjugate acid of the nitroamine by halide ion, the nitrite ion displaced then diazotizing more nitroamine which in turn gives rise to a more rapid displacement of nitrite ion by halide ion. The intermediacy of a diazonium ion of type **107** was confirmed by conducting both reactions in the presence of β -naphthol; the expected azocompounds (**108**) were formed in good yield.^{351, 389}

In contrast to the behavior of the 2-acetamido compound, nitration of 2-benzenesulfonamidodibenzothiophene¹⁵⁴ and 2-benzamidobenzo-
thiophene⁴⁰⁸ results in the production, after hydrolysis, of 2-amino-3-
nitrodibenzothiophene. This nitroamine was different from **103** and



(107)

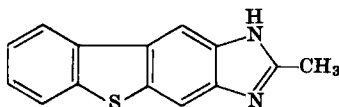
X = Cl or Br



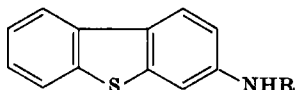
(108)

X = Cl or Br

formed the imidazole (**109**) upon reduction in acetic acid, thus confirming
ortho-nitration.¹⁵⁴



(109)

(110a) R = COCH₃

(110b) R = COPh

(110c) R = CO₂-n-Pr

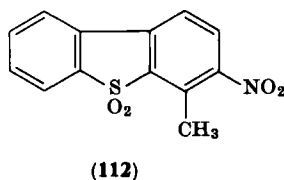
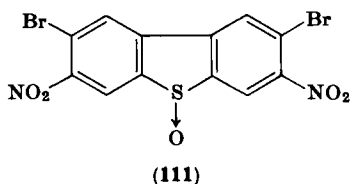
Three derivatives of 3-aminodibenzothiophene, **110a**,¹⁵⁵ **110b**,⁴⁰⁸
and **110c**,¹⁵⁵ have been nitrated, and in each case substitution occurred
in the 4-position. Hydrolysis of the products yielded 3-amino-4-nitro-
dibenzothiophene, which was different from the previous two nitro-
amines and which formed an imidazole different from both **104** and **109**.
Deamination of this nitroamine via diazotization gave a small amount of
4-nitrodibenzothiophene.¹⁵⁵ An alternative synthesis of the 4-nitro
compound is described later. The spectroscopic techniques used above
by Sawicki were later extended to determine the positions of substitution
in dibenzoselenophene, in this case by comparison with the above-
established derivatives of dibenzothiophene.^{147, 151}

Nitration of 2-bromodibenzothiophene 5,5-dioxide gave a mononitro
compound tentatively assumed to be the 7-nitro isomer; enlarged
preparative details of the known 8-nitro-2-bromodibenzothiophene
were also described.²³⁵

Nitration of 2,8-dibromodibenzothiophene gave a product which was
assigned structure **111**, while attempts to nitrate 2,8-dibromodibenzo-
thiophene 5,5-dioxide were unsuccessful.³⁹³ The preparation of 2,7-

⁴⁰⁸ H. Gilman and G. R. Wilder, *J. Amer. Chem. Soc.* **77**, 3920 (1955).

dinitrodibenzothiophene is described in Section IV, D, and the nitration of 4-methoxydibenzothiophene in Section VI, D.



As mentioned earlier, oxidation of dibenzothiophene to either the sulfoxide or sulfone causes electrophilic attack to occur at the 3-position rather than at the normal 2-position.¹ This trend is further exemplified by the behavior of 4-methyldibenzothiophene which is nitrated in the 2-position (26%), while nitration of 4-methyldibenzothiophene 5,5-dioxide occurs in the 3-position yielding **112**.⁸⁹ The structures of both of these products were deduced from their NMR spectra.

An alternative synthesis of 4-nitrodibenzothiophene involves heating 2-amino-2'-nitrodiphenyl sulfide in a sealed tube at 190° (20%). The reaction probably proceeds via homolytic cleavage of the derived diazonium ion which could have been formed from nitrous acid liberated during the formation of phenothiazines, which were also detected. Similarly, 2-methyl-4-nitrodibenzothiophene is formed from 2-amino-2'-nitro-4'-methyldiphenyl sulfide (10%), and in this case the intermediacy of the diazonium ion was further indicated in that the same material was obtained by pyrolysis of the separately prepared diazonium salt of the sulfide.¹⁵⁶ Although yields are poor in this reaction, it nevertheless represents the only route to substituted dibenzothiophenes containing a nitro substituent in the 4-position and as such is worthy of further attention.

2. Aminodibenzothiophenes

The synthesis of 1-aminodibenzothiophene by reduction of the 1-nitro compound with hydrogen and Raney nickel (57%)³⁸⁹ completes the series of monoaminodibenzothiophenes.¹ A synthesis of 2-aminodibenzothiophene 5,5-dioxide from the corresponding 2-bromo compound has been described involving heating with ammonium hydroxide and copper at 200° (66%).⁴⁰⁹ 8-Bromo-2-aminodibenzothiophene has been prepared by catalytic reduction of the corresponding nitro compound

⁴⁰⁹ S. Natori, M. Ito, and T. Nakagome, *Pharm. Bull.*, 548 (1957).

(45%).²³⁵ 3-Aminodibenzothiophene is prepared by reduction of 3-nitrodibenzothiophene 5-oxide with stannous chloride at room temperature,^{395, 410} however, some difficulty has been experienced in repeating this reaction and as a result a slightly modified procedure has been described.⁸⁵ Reaction of 3-aminodibenzothiophene with trifluoroacetic anhydride, in benzene, yields 3-trifluoroacetamidodibenzothiophene in high yield.⁴¹¹ Nitration of 2-bromodibenzothiophene 5,5-dioxide probably occurs in the 7-position; reduction of this material with tin and hydrochloric acid gives the corresponding amine (67%).²³⁵

Both 2- and 3-aminodibenzothiophene are structurally similar to benzidine and are potential carcinogens to man.^{412, 413} The carcinogenicity of these two amines, their *N*-acyl, alkyl, and fluoro derivatives and the corresponding sulfoxides and sulfones has been correlated with the overall electron-donating properties of these molecules, which have been determined by measuring their charge-transfer spectra with chloranil in acetonitrile,^{163, 164} measuring their redox potentials polarographically,¹⁶⁴ and by the acridine test.¹⁶⁴ Several amino derivatives of dibenzothiophene have been specifically prepared for testing as potential carcinogens. For example, both 2-amino- and 3-aminodibenzothiophene have been condensed with aromatic aldehydes to yield the benzalamino derivatives, reacted with phthalic anhydride to give the *o*-carboxybenzoylamido compounds and with alkylcarbonates to give the 2- and 3-alkylcarbamates.^{135, 414, 415} Likewise, condensation of both amines with arylsulfonic acids yields the corresponding sulfonamides and sulfanilamides.^{414, 416} Although carcinogenic activity varied over these compounds, all derivatives of 2- and 3-aminodibenzothiophene should be handled with caution.⁴¹²

Twenty-five dibenzothiophenes, composed mainly of amino and acetamidodibenzothiophenes and their sulfoxides and sulfones, have been tested for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Mycobacterium tuberculosis*. Activity was found against the latter with 2- and 3-aminodibenzothiophene in synthetic culture media, but the effect was reversed by the addition of serum.^{409, 415}

⁴¹⁰ E. V. Brown and R. Isbrandt, *J. Med. Chem.* **14**, 84 (1971).

⁴¹¹ E. Sawicki and F. E. Ray, *J. Amer. Chem. Soc.* **75**, 2266 (1953).

⁴¹² J. H. Weisburger and E. K. Weisburger, *Clin. Pharmacol. Ther.* **4**, 110 (1963).

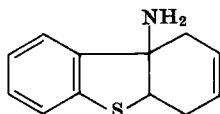
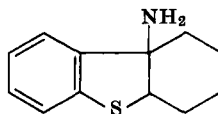
⁴¹³ J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Res.* **15**, 188 (1955); *Chem. Abstr.* **49**, 16178 (1955).

⁴¹⁴ E. Sawicki and H. S. Greene, *J. Amer. Chem. Soc.* **75**, 1752 (1953).

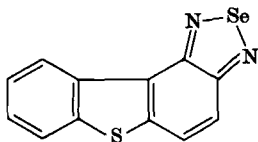
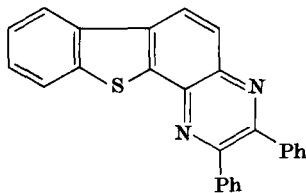
⁴¹⁵ K. A. Allen, J. Cymerman-Craig, and A. A. Diamantis, *J. Chem. Soc.*, 234 (1954).

⁴¹⁶ E. Sawicki, *J. Amer. Chem. Soc.* **76**, 664 (1954).

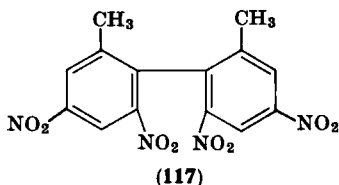
Two novel monoaminodibenzothiophenes, 9b-amino-1,4,4a,9b-tetrahydrodibenzothiophene (**113**) and 9b-amino-1,2,3,4,4a,9b-hexahydrodibenzothiophene (**114**) have been synthesized from the corresponding carboxylic acid sulfones **32** and **33** by treatment with sodium methoxide and bromine followed by reduction of the resultant sulfone carbamates with LAH. *N*-Alkylation of both **113** and **114** gives compounds which possess CNS depressant activity.³¹⁵

**(113)****(114)**

The studies by Gilman *et al.* and Sawicki on the nitration of derivatives of 2- and 3-aminodibenzothiophene have made available for the first time diaminodibenzothiophenes in which both amine functions are present in the same ring. Reduction of 2-amino-1-nitrodibenzothiophene with stannous chloride yields 1,2-diaminodibenzothiophene (80%).¹⁵⁴ As expected this compound reacts readily with acetic acid to give the imidazole (**104**) and with selenium dioxide to give the selenadiazole (**115**). Reduction of 2-amino-3-nitrodibenzothiophene in the presence of acetic acid yields the imidazole (**109**)¹⁵⁴ and by conducting this reaction in the absence of acetic acid 2,3-diaminodibenzothiophene should be readily accessible. A similar reduction of 3-amino-4-nitrodibenzothiophene yields 3,4-diaminodibenzothiophene (60%).¹⁵⁵ In addition to the typical reactions described above for the 1,2-diamino compound, 3,4-diaminodibenzothiophene condenses with benzil to give the quinoxaline (**116**) (45%).¹⁵⁵ The chlorination and bromination of derivatives of 2- and 3-aminodibenzothiophene is discussed in Sections VI, C, 2, and 3.

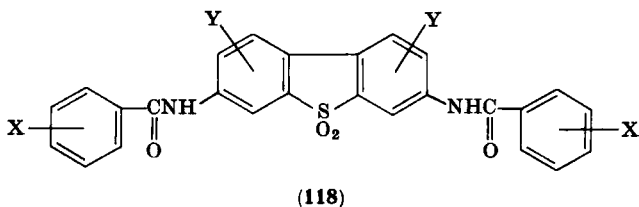
**(115)****(116)**

3,7-Diamino-1,9-dimethyldibenzothiophene has been synthesized by reduction of 4,4',6,6'-tetranitro-2,2'-ditolyl (117) with ammonium or sodium sulfide at 5°. By conducting the reaction at 60° the corresponding dibenzofuran was formed, but no yields were given.³⁵³



A considerable body of industrial patent literature exists relating to 3,7-diaminodibenzothiophenes. Unfortunately many otherwise interesting compounds appear without details of preparation or proof of structure; therefore, only brief coverage of this material is given below.

Diazotization of 3,7-diaminodibenzothiophene 5,5-dioxide, which has the trivial name of benzidine sulfone, followed by coupling with phenols, anilines, or arylsulfonic acids gives bis-azo dyes varying in color from red-brown to blue. These dyes are useful for the coloring of plastics and cellulose.^{392, 417-422} A second class of compounds based on 3,7-diaminodibenzothiophene 5,5-dioxide and having the general structure 118, is formed by benzylation in the presence of a tertiary base or guanidine. These compounds are used as fluorescent whiteners for cotton and poly-



⁴¹⁷ T. Kawai and T. Veda, *Yakugaku Zasshi* **80**, 1651 (1960).

⁴¹⁸ E. Fischer and F. Muris, German Patent 918,634 (1954); *Chem. Abstr.* **51**, 2302 (1957).

⁴¹⁹ E. Fischer, German Patent 889,739 (1953); *Chem. Abstr.* **50**, 11678 (1956).

⁴²⁰ H. Z. Lecher and S. M. Tsang, U.S. Patent 2,752,333 (1956); *Chem. Abstr.* **51**, 15140 (1957).

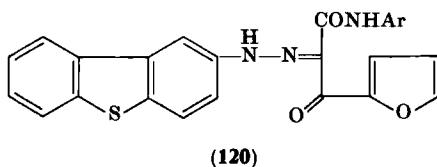
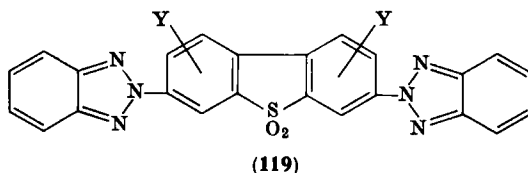
⁴²¹ O. F. Schulz and P. H. Fickel, British Patent 695,334 (1953); *Chem. Abstr.* **48**, 386 (1953).

⁴²² D. I. Randall and W. Schmidt-Nickels, U.S. Patent 2,773,873 (1956); *Chem. Abstr.* **51**, 14279 (1957).

amide materials, usually by incorporation into detergents^{330, 392, 420, 422-439, 439a} and as photographic plate sensitizers.⁴⁴⁰ A third class of compounds is formed by diazotization of 3,7-diaminodibenzothiophene 5,5-dioxide and coupling with arylamines followed by oxidative cyclization yielding triazolo compounds of type **119**.⁴⁴¹⁻⁴⁴⁷ These compounds have a

- ⁴²³ H. Z. Lecher, D. R. Eberhart, M. Scalera, and W. S. Forster, British Patent 696,038 (1953); *Chem. Abstr.* **48**, 1017 (1953).
⁴²⁴ P. G. Hendrix, U.S. Patent 2,619,470 (1952); *Chem. Abstr.* **47**, 4100 (1953).
⁴²⁵ R. S. Long and D. W. Hein, U.S. Patent 2,671,790 (1954); *Chem. Abstr.* **49**, 4025 (1955).
⁴²⁶ M. Scalera and W. S. Forster, U.S. Patent 2,573,652 (1951); *Chem. Abstr.* **46**, 3572 (1952).
⁴²⁷ H. Z. Lecher and D. R. Eberhart, U.S. Patent 2,619,490 (1952); *Chem. Abstr.* **46**, 9365 (1952).
⁴²⁸ M. Scalera and D. R. Eberhart, U.S. Patent 2,563,493 (1951); *Chem. Abstr.* **46**, 271 (1952).
⁴²⁹ E. M. Robertson and J. A. Van Allan, U.S. Patent 2,870,011 (1959); *Chem. Abstr.* **53**, 12902 (1959).
⁴³⁰ H. B. Freyermuth and W. W. Williams, U.S. Patent 2,911,415 (1959); *Chem. Abstr.* **54**, 6147 (1960).
⁴³¹ N. L. Anderson, U.S. Patent 2,845,423 (1958); *Chem. Abstr.* **53**, 1763 (1959).
⁴³² A. Cerniani and G. Cordella, *Ric. Sci.* **26**, 3352 (1956).
⁴³³ Sterling Drug Inc., British Patent 859,891 (1961); *Chem. Abstr.* **60**, 13451 (1964).
⁴³⁴ F. Marschall, U.S. Patent 3,031,460 (1962); *Chem. Abstr.* **57**, 13937 (1962).
⁴³⁵ W. S. Forster, U.S. Patent 3,226,247 (1965); *Chem. Abstr.* **64**, 9860 (1966).
⁴³⁶ R. B. Wearn, P. T. Vitale, and G. F. Marion, U.S. Patent 3,257,324 (1966); *Chem. Abstr.* **65**, 9091 (1966).
⁴³⁷ Procter and Gamble Co., British Patent 1,045,977 (1966); *Chem. Abstr.* **66**, 20244 (1967).
⁴³⁸ H. E. Wixon, U.S. Patent 3,346,502 (1967); *Chem. Abstr.* **68**, 60496 (1968).
⁴³⁹ A. Dorlars and O. Neuner, British Patent 1,155,229 (1969); *Chem. Abstr.* **71**, 92665 (1969).
^{439a} American Cyanamid Co., British Patent 900,803 (1962); *Chem. Abstr.* **57**, 11416 (1962).
⁴⁴⁰ N. W. Kalenda, Def. Publ. U.S. Patent Office 768,921 (1969); *Chem. Abstr.* **71**, 8442 (1969).
⁴⁴¹ H. Foster, *J. Amer. Chem. Soc.* **82**, 3780 (1960).
⁴⁴² W. W. Williams and H. B. Freyermuth, U.S. Patent 2,927,866 (1960); *Chem. Abstr.* **54**, 16852 (1960).
⁴⁴³ W. W. Williams and H. B. Freyermuth, U.S. Patent, 2,733,165 (1956); *Chem. Abstr.* **50**, 7471 (1956).
⁴⁴⁴ A. E. Siegrist, U.S. Patent 2,719,155 (1955); *Chem. Abstr.* **50**, 4525 (1956).
⁴⁴⁵ B. G. Buell and R. S. Long, U.S. Patent 3,049,438 (1962); *Chem. Abstr.* **59**, 6555 (1963).
⁴⁴⁶ B. G. Buell and R. S. Long, U.S. Patent 3,058,989 (1962); *Chem. Abstr.* **59**, 6555 (1963).
⁴⁴⁷ J. Brunken, E. J. Poppe, and W. Schindler, East German Patent 39,717 (1965); *Chem. Abstr.* **64**, 2909 (1966).

similar spectrum of uses as compounds of type **118**. Finally, coupling of the diazonium compounds derived from either 2- or 3-aminodibenzothiophene, or their sulfones, with furoylacetarylides yields azoic dyes of



type **120** which are useful for coloring cotton and viscose rayon.^{432, 448} In both **118** and **119** Y is usually $-\text{SO}_3\text{H}$, formed by excess sulfonation during the synthesis of the starting material from benzidine and oleum (Section IV, D).

An analytical color test for the detection of Pb, Mn, Co, Cr, and Cu ions uses 3,7-diaminodibenzothiophene 5,5-dioxide.⁴⁴⁹

3. Miscellaneous Nitrogen Derivatives

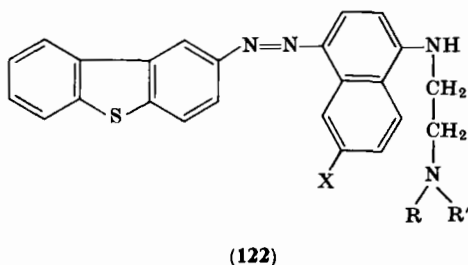
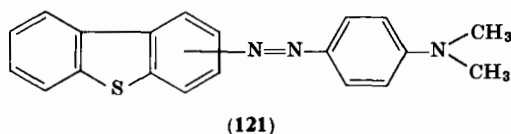
a. *Nitriles*. 2-Cyanodibenzothiophene is the only known nuclear-substituted nitrile of dibenzothiophene.^{1, 352} It has been synthesized by treatment of 2-bromodibenzothiophene with cuprous cyanide (35%)¹ and this method could now be used to prepare the other isomers. Alternatively, the four monoaminodibenzothiophenes are available and could be employed in a standard Sandmeyer conversion. Diazotization of 3,7-diaminodibenzothiophene 5,5-dioxide followed by treatment with potassium thiocyanate yields the corresponding bis-thiocyanato compound.³⁹⁸ Treatment of 4-chloromethyldibenzothiophene with potassium cyanide affords the 4-cyanomethyldibenzothiophene (81%).⁴⁰⁴

b. *Azo compounds*. The four monoaminodibenzothiophenes have been diazotized and coupled with *N,N*-dimethylaniline, yielding the azo compounds (**121**) (20–60%). They were all found to be inactive as rat hepatocarcinogenic agents.⁴¹⁰ Coupling 2-aminodibenzothiophene with aminonaphthalenes gives compounds of general formula **122** which

⁴⁴⁸ A. Cerniani, *Ric. Sci.* **26**, 3089 (1956).

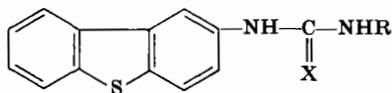
⁴⁴⁹ T. Kawai and T. Veda, *Yakugaku Zasshi* **80**, 1651 (1960).

have been patented as antiparasitic agents.⁴⁵⁰ The diazonium salt derived from 3,7-diaminodibenzothiophene 5,5-dioxide has been coupled with a wide range of compounds giving azo dyes (Section VI, E, 2) and the ionization constants of this salt have been determined by rapid potentiometric titration.⁴⁵¹



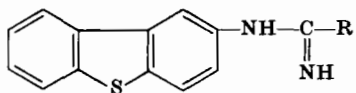
Both 2- and 3-azidodibenzothiophene have been prepared by the action of sodium azide on the appropriate diazonium compound ($> 90\%$).¹⁵¹ Heating 2-azidodibenzothiophene in polyphosphoric acid yields 2,2'-azodibenzothiophene (54%).⁹⁴

c. *Guanidines, Thioureas, and Amidines.* Reaction of 2-aminodibenzothiophene with cyanamide afforded 2-guanidinodibenzothiophene (**123a**). The product was isolated as the carbonate by passing CO_2 through an ethereal solution of the base.⁴⁵² Preliminary tests with the low virulence strain "Valee" of *Mycobacterium tuberculosis* showed **123a** to be active as a tuberculostatic agent at dilutions as low as $1:1 \times 10^5$. Condensation of 2,8-diacetyldibenzothiophene with aminoguanidine



(123a) R = H, X = NH

(123b) R = Alkyl or aryl, X = S



(124)

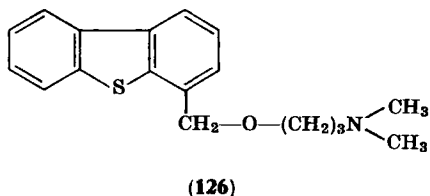
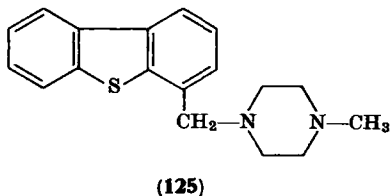
⁴⁵⁰ E. F. Elslayer, D. F. Worth, D. B. Capps, and L. M. Werbel, U.S. Patent 3,139,421 (1964); *Chem. Abstr.* **61**, 6972 (1964).

⁴⁵¹ B. A. Porai-Koshits and A. B. Torchin, *Zh. Org. Khim.* **2**, 2238 (1966); *Chem. Abstr.* **66**, 85551 (1967).

⁴⁵² V. Grinsteins and G. Cerna, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 519 (1962); *Chem. Abstr.* **59**, 6340 (1963).

gives the corresponding, cardioactive, 2,8-diacetyldibenzothiophene diguanylhydrazone.⁴⁵³ A series of 17 thioureas of general formula **123b** have been prepared in high yield by reacting 2-aminodibenzothiophene with variously substituted aryl and alkylisothiocyanates. 2-Aminodibenzothiophene 5,5-dioxide failed to react under similar conditions.²⁵³ Reaction of the ammonium benzene sulfonate, derived from either 2-aminodibenzothiophene or its sulfone and benzenesulfonic acid, with (*o*-, *m*-, and *p*-alkyl, halo, alkoxy or nitro)benzonitrile or alkyl nitriles gave amidines of the general type **124** in high yield.²⁵³ The thioureas (**123b**) and the amidines (**124**) were prepared as potential antiviral or tuberculostatic agents.

d. *Nitrovinyl and Aminoalkyl Derivatives.* The aldehydes of dibenzothiophene condense readily with nitromethane yielding nitrovinyl compounds. In this manner 2-(2'-nitrovinyl)- and 4-methyl-3-(2'-nitrovinyl)dibenzothiophene^{454, 455} and 1,4-dimethyl-2-(2'-nitrovinyl)dibenzothiophene²⁵¹ have been synthesized. Reduction of these derivatives with LAH gives the corresponding aminoethyl compounds,^{251, 454, 455} which have been used in the synthesis of the corresponding isoquinolines (Section VI, F, 1). Reduction of 4-cyanomethyl dibenzothiophene with LAH yields the 4-aminoethyl compound, which possesses analgesic, antibacterial, and antifungal activity.⁴⁰⁶ A large series of alkylamines and alkoxy amines have been synthesized in the 4-position of dibenzothiophene following the discovery of a range of physiological responses produced by such compounds. Compounds of type **125** are produced by reduction of the appropriate 4-dibenzothiophenecarboxamide with LAH,^{404-406, 456} while those of type **126** are formed by the reaction of 4-hydroxymethyl dibenzothiophene with an ω -aminoalkyl halide.⁴⁵⁷



⁴⁵³ Farbenfabriken Bayer, British Patent 1,053,035 (1966); *Chem. Abstr.* **66**, 94825 (1967).

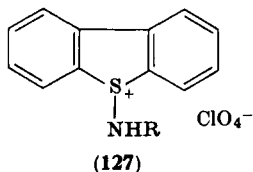
⁴⁵⁴ E. Campaigne, L. Hewitt, and J. Ashby, *Chem. Commun.*, 598 (1969).

⁴⁵⁵ E. Campaigne and J. Ashby, *J. Heterocycl. Chem.* **6**, 875 (1969).

⁴⁵⁶ M. Protiva and K. Pelz, Czech. Patent 133,124 (1969); *Chem. Abstr.* **73**, 98941 (1970).

⁴⁵⁷ M. Protiva, K. Pelz, and F. Hradil, Czech. Patent 133,123 (1969); *Chem. Abstr.* **73**, 98937 (1970).

e. *5-Aminodibenzothiophenium Salts*. Reaction of 5-methoxydibenzothiophenium perchlorate (Section VI, D) with aliphatic amines gives dibenzothiophenium salts of type **127**. The reaction proceeds via nucleophilic attack by the amine on the sulfur atom, with displacement of methoxide. Aniline and hydrazine did not react.³⁶⁰



F. SIDE-CHAIN CARBONYLS

1. Aldehydes

Two approaches to the synthesis of the aldehydes of dibenzothiophene have been made. The most successful method, used by Campaigne *et al.*, involves treatment of the appropriate bromodibenzothiophene with butyllithium and dimethylformamide; yields are generally high. Employing this method the following aldehydes have been obtained: 2-dibenzothiophenecarboxaldehyde (71%) (m.p. 104°–105°), the 3-carboxaldehyde (41%), and 2,8-dibenzothiophenedicarboxaldehyde (69%);⁸⁵ 4-methyl-2-dibenzothiophenecarboxaldehyde (77%) and the corresponding 3-carboxaldehyde (95%),^{89, 454} and 4-methoxy-1-dibenzothiophenecarboxaldehyde (88%).⁹⁰

The formylating reagent α, α -dichloromethyl butyl ether described by Rieche⁴⁵⁸ has been employed by three groups^{91, 92, 459} for the formylation of dibenzothiophenes. The results are generally disappointing, mixtures of isomers occurring. All of the reported reactions were conducted at 0° and in view of the fact that this reagent has been shown to be effective at -50° ³¹¹ much lower temperatures would probably give greater positional selectivity. Using this reagent on dibenzothiophene in methylene chloride, with stannic chloride as catalyst, Elmes and Swan obtained a mixture of the 2- and 4-aldehydes (3 : 2 by NMR) (51%).⁹² Purification by fractional crystallization gave 4-dibenzothiophenecarboxaldehyde (12%) (m.p. 124°–125°) and an unspecified quantity of the 2-aldehyde (m.p. 102°–102.5°). The structure of both compounds was

⁴⁵⁸ A. Rieche, H. Gross, and E. Hoft, *Chem. Ber.* **93**, 88 (1960).

⁴⁵⁹ G. Vasiliu, A. Gioaba, and O. Maior, *An. Univ. Bucuresti, Ser. Stiint. Natur., Chim.* **15**, 33 (1966); *Chem. Abstr.* **70**, 77686 (1969).

confirmed by NMR analysis and oxidation to the known 2- and 4-carboxylic acids. Independently, Vasiliu and co-workers⁴⁵⁹ treated dibenzothiophene with the chloro ether in carbon disulfide, using titanium tetrachloride as catalyst and obtained 2-dibenzothiophenecarboxaldehyde as sole product (9%) (m.p. 126°–127°). Again the structure of the material was confirmed by oxidation to the carboxylic acid. Despite the fact that the previous two groups had reported the melting point of the 2-aldehyde to be 20° lower, Vasiliu's must be taken as correct. Moreover, the derived 2-carboxylic acid described by Vasiliu melted 20° higher than that described by Elmes and Swan, which is in closer agreement with the revised melting point of highly purified 2-dibenzothiophenecarboxylic acid (Section VI, G, 1). Rieche formylation of 6,9-dimethyl-1,2,3,4-tetrahydrodibenzothiophene gave an inseparable mixture of the 7- and 8-aldehydes, NMR showing that the 7-aldehyde predominated.⁹¹ By the same method 1,4-dimethyldibenzothiophene gave a mixture of the 2- and 3-aldehydes from which 1,4-dimethyl-2-dibenzothiophenecarboxaldehyde was obtained by crystallization (55%).⁹¹ Both 1,4-dimethyldibenzothiophene 5,5-dioxide and its tetrahydro derivative failed to react under the above conditions.²⁵⁰

1-Dibenzothiophenecarboxaldehyde has not been reported but should be readily formed from 1-bromodibenzothiophene via the lithium exchange route as described above. Likewise a better route to 4-dibenzothiophenecarboxaldehyde may be via the readily formed 4-lithiodibenzothiophene (Section VI, H, 1).

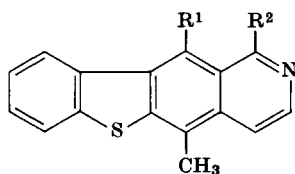
The usual range of reactions has been recorded for the aldehydes of dibenzothiophene. Oxidation yields the corresponding acid,^{92, 459} reduction with LAH the corresponding alcohol,⁸⁵ reduction under Huang–Minlon conditions the corresponding methyl compound,^{85, 89} and two examples of the Cannizarro reaction have been described.^{85, 89}

The sulfur analogs of the indole alkaloids ellipticine and olivacine and related heterocycles have been synthesized by standard isoquinoline methods from the above aldehydes. For example, condensation of 1,4-dimethyl-2-dibenzothiophenecarboxaldehyde with aminoacetaldehyde diethyl acetal followed by cyclization in polyphosphoric acid yielded thiaellipticine⁹¹ (**128a**), and condensation of 4-methyl-3-dibenzothiophenecarboxaldehyde with nitromethane followed by reduction and Bischler–Napieralski cyclization gave thiaolivacine (**128b**).^{454, 455} These compounds are of current interest as antitumor agents.^{92, 250, 251, 460, 461}

⁴⁶⁰ J. M. Swan, *Aust. J. Sci.* **29**, 435 (1967).

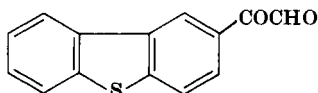
⁴⁶¹ E. Campaigne, J. Ashby, and S. W. Osborn, *J. Heterocycl. Chem.* **6**, 885 (1969).

Oxidation of 2-acetyldibenzothiophene with selenium dioxide in dioxane gave 2-dibenzothiopheneglyoxylaldehyde (**129**) (27%, pentahydrate), which condensed with 2 moles of *p*-aminobenzoic acid to yield the corresponding aminal.^{462, 463} Both compounds possessed antiviral activity.



(128a) $R^1 = \text{CH}_3$, $R^2 = \text{H}$

(128b) $R^1 = \text{H}$, $R^2 = \text{CH}_3$



(129)

2. Ketones

a. *Acetyldibenzothiophenes*. 2-Acetyldibenzothiophenes were first isolated by Gilman³⁹⁴ by treatment of dibenzothiophene in carbon disulfide with acetyl chloride and aluminum chloride (70%). Burger *et al.*, repeating this work under a variety of conditions,^{228, 229} isolated a mixture of acetyl compounds (70%) from which they were able to obtain 2-acetyldibenzothiophene (25%) and a small quantity of the 4-acetyl isomer. Andreeva and Koton^{407, 464} have reported that conducting the acetylation in benzene or toluene yields an inseparable mixture of 2- and 3-acetyldibenzothiophene, while use of either carbon disulfide or nitrobenzene yields a similar mixture from which the 2-acetyl compound was isolated by solvent extraction (20%). The authors offered no proof of identity of the supposed 3-acetyl compound. The use of stannic chloride as catalyst for the acetylation has been reported by no yields were recorded.^{462, 463} The isolation of 4-acetyldibenzothiophene by Burger represented the first electrophilic substitution of dibenzothiophene in the 4-position; this result has now been paralleled by the formylation reaction reported by Elmes and Swan (Section VI, F, 1). The kinetics of the Friedel-Crafts acetylation of dibenzothiophene in nitroethane have been studied; the reaction proceeds approximately five times faster than with toluene as substrate.^{465, 466}

⁴⁶² E. L. Anderson, J. E. Casey, Jr., M. Emas, E. E. Force, E. M. Jensen, R. S. Matz, and D. E. Rivard, *J. Med. Chem.* **6**, 787 (1963).

⁴⁶³ E. L. Anderson, U.S. Patent 3,083,201 (1963); *Chem. Abstr.* **59**, 6367 (1963).

⁴⁶⁴ I. V. Andreeva and M. M. Koton, *J. Gen. Chem. USSR* **27**, 1079 (1957); *Chem. Abstr.* **53**, 5230 (1959).

⁴⁶⁵ P. Finocchiaro, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania 4th Ser.* **9** (9), 573 (1969); *Chem. Abstr.* **72**, 66115 (1970).

⁴⁶⁶ P. Finocchiaro, *Ann. Chim. (Rome)* **59**, 787 (1969).

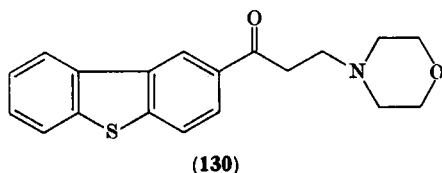
The most convenient method of preparation of acetyldibenzothiophenes is via treatment of the appropriate lithio derivative with *N,N*-dimethylacetamide. In this way 2-acetyl- (92%) and 3-acetyldibenzothiophene (44%) have been prepared.⁸⁵ Using this method the relatively inaccessible 4-acetyl and the unknown 1-acetyl isomers should become readily available.

Friedel-Crafts acetylation of 4-methyldibenzothiophene yields 2-acetyl-4-methyldibenzothiophene (33%), which readily undergoes the Mannich reaction.⁸⁹

Oxidation of 2-acetyldibenzothiophene with peracetic acid yields the corresponding sulfone (86%) and with sodium hypodite, 2-dibenzothiophenecarboxylic acid.⁴⁵⁹ A color reaction for 2-acetyldibenzothiophene has been reported.⁴⁶⁷

b. *γ*-Oxodibenzothiophenebutyric Acids. Oxodibenzothiophenebutyric acids are discussed in Section VI, G, 2.

c. *Miscellaneous Ketones*. 4-Veratrotyldibenzothiophene has been isolated as an expected by-product (5%) in the reaction of dibenzothiophene and butyllithium with carbon dioxide.⁴⁶⁸ Friedel-Crafts acylation of dibenzothiophene with β -chloropropanoyl chloride occurs in the 2-position. Replacement of the chlorine with amines yielded Mannich compounds of type **130**.⁴⁶⁹ The acetylation of 1,2,3,4-tetrahydrodibenzothiophene has been described earlier (Section V, B, 2).



Friedel-Crafts diacylation of dibenzothiophene with 7-oxo-7*H*-benzo[*d,e*]anthracene-3-carbonyl chloride, followed by ring closure in molten sodium chloride-aluminum chloride, is reported to yield **131** which is claimed to be useful as an orange dyestuff.⁴⁷⁰ No evidence for the structure of **131** was presented although analogous succinylation studies (Section VI, G, 2) would indicate that the structure is correct.

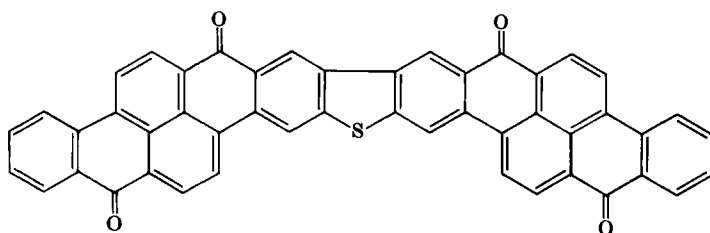
⁴⁶⁷ E. Sawicki, J. Noe, and T. W. Stanley, *Mikrochim. Acta*, 286 (1960).

⁴⁶⁸ H. Gilman and D. L. Esmay, *J. Amer. Chem. Soc.* **75**, 233 (1953).

⁴⁶⁹ N. Wasserman, M. Calarasanu, and R. Waitman, *Rev. Chim. (Bucharest)* **11**, 349 (1960); *Chem. Abstr.* **58**, 3418 (1963).

⁴⁷⁰ W. Schmidt-Nickels, U.S. Patent 2,562,872 (1951); *Chem. Abstr.* **46**, 11695 (1952).

A similar reaction of dibenzothiophene with 1,8-naphthoylenebenzimidazole-4-carbonyl chloride has also been described.⁴⁷¹

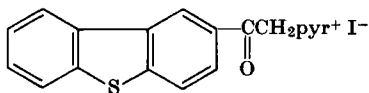


(131)

G. ACIDS

1. Nuclear Carboxylic Acids

The synthesis of the four monocarboxylic acids of dibenzothiophene has been recorded in the previous review.¹ However, several modified preparations have since been described. Ethyl 1-dibenzothiophenecarboxylate has been synthesized from 2-allylbenzo[*b*]thiophene (Section IV, B, 1); hydrolysis afforded the 1-acid (57% overall). In a similar manner, 3-methyl-1-dibenzothiophenecarboxylic acid was obtained from the appropriately substituted allyl compound.³¹¹ This method is now the preferred way of introducing a carbon-containing substituent into the 1-position of dibenzothiophene. 2-Dibenzothiophenecarboxylic acid has been prepared by oxidation of the corresponding aldehyde^{92, 459} or by sodium hypoiodite oxidation of the corresponding acetyl compound.⁴⁵⁹ Reaction of 2-acetyldibenzothiophene with anhydrous pyridine and iodine yields the acetyl pyridinium salt (132) (92%), hydrolysis of which yields the 2-acid (85%). The same sequence has been carried out on 2-acetyldibenzothiophene 5,5-dioxide.⁴⁵⁹ The most efficient method of preparing the 2-acid is via carbonation of 2-lithio-



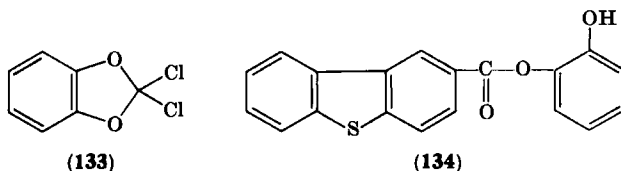
(132)

dibenzothiophene (97%).⁸⁵ Until recently the accepted melting point for 2-dibenzothiophenecarboxylic acid was 253°–255°;³⁹⁴ however, repeated crystallization from methanol raises this to 276°–278°.⁸⁵

⁴⁷¹ W. Schmidt-Nickels, U.S. Patent 2,820,036 (1958); *Chem. Abstr.* **52**, 8573 (1958).

Melting points throughout this 23° range have been recorded which encompass the melting point of 4-dibenzothiophenecarboxylic acid (261°–263°¹). The recorded melting points of 2-dibenzothiophenecarboxaldehyde also vary over a 20° range, which again lies on either side of the melting point of 4-dibenzothiophenecarboxaldehyde (Section VI, F, 1). Thus, great care is needed in characterizing these compounds.

Reaction of pyrocatechol dichloromethylene acetal⁴⁷² (**133**) with dibenzothiophene in the presence of titanium tetrachloride yields *o*-hydroxyphenyl-2-dibenzothiophenecarboxylate (**134**) (100%).⁴⁵⁹ This reaction is closely related to the Rieche formylation of dibenzothiophene (Section VI, F, 1) in which a mixture of 2- and 4-dibenzothiophenecarboxaldehyde was obtained. The complete absence of the 4-isomer in this reaction may be due to steric effects at the 4-position between the sulfur atom and the bulky reagent. Hydrolysis of **134** yields 2-dibenzothiophenecarboxylic acid (70%).⁴⁵⁹ 4-Methyl-3-dibenzothiophenecar-



boxylic acid has been prepared by carbonation of the corresponding lithio compound (92%).⁸⁹ Diazotization of 3-amino-2-(phenylthio)benzoic acid followed by treatment with cuprous chloride yields a mixture of the expected chloro compound and 4-dibenzothiophenecarboxylic acid (30%).^{404, 473} A large range of amides, alkylamines, and aminoalkyl esters derived from the 4-dibenzothiophenecarboxylic acid have been reported variously to possess hypotensive, vasodilating, antibacterial, diuretic, local anesthetic, or antifungal activity.^{404–406, 456, 457, 474}

There is still no efficient synthesis of 3-dibenzothiophenecarboxylic acid. The only recorded preparation is via metallation of dibenzothiophene with phenylcalcium iodide followed by carbonation,¹ but the yield was poor. The successful use of 3-lithiodibenzothiophene to give the 3-aldehyde⁸⁵ indicates that 3-bromodibenzothiophene would probably be the best precursor of the 3-acid. Both 1,4,4a,9b-tetrahydrodibenzo-

⁴⁷² H. Gross, J. Rusche, and M. Mirsch, *Chem. Ber.* **96**, 1382 (1963).

⁴⁷³ K. Pelz, I. Ernest, E. Adlerova, J. Metysova, and M. Protiva, *Collect. Czech. Chem. Commun.* **33**, 1852 (1968).

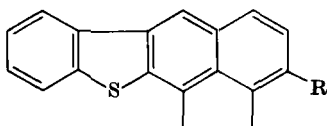
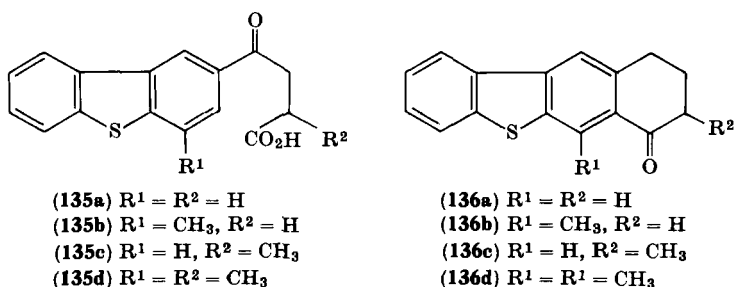
⁴⁷⁴ P. E. Thompson, D. F. Walker, and M. C. Dunn, *J. Amer. Pharm. Ass.* **42**, 647 (1953).

thiophene 5,5-dioxide and 1,2,3,4,4a,9b-hexahydrodibenzothiophene 5,5-dioxide bearing a carboxy group at C-9b, **32** and **33**, respectively, have been described earlier (Section IV, B, 2).

3,4-Dibenzothiophenedicarboxylic anhydride and 1,2,3,4-tetrahydro-3,4-dibenzothiophenedicarboxylic acid have been synthesized from 3-vinylbenzo[*b*]thiophene (Section IV, B, 2). 1,4-Dimethyl-2,3-dibenzothiophenedicarboxylic acid is formed via oxidation of the trioxide of thiaellipticine (**128a**)²⁵⁰ (Section VI, F, 1).

2. γ -Oxo-dibenzothiophenebutyric Acids

Friedel-Crafts acylation of dibenzothiophene with succinic anhydride is known to occur in the 2-position, yielding γ -oxo-2-dibenzothiophenebutyric acid (**135a**). Subsequent Wolff-Kishner reduction and internal cyclization yields 7-keto-7,8,9,10-tetrahydrobenzo[*b*]naphtho[2,3-*d*]thiophene (**136a**).^{475, 476} This reaction has been extended to 4-methyldibenzothiophene, which likewise gives the 2-substituted keto acid (**135b**)



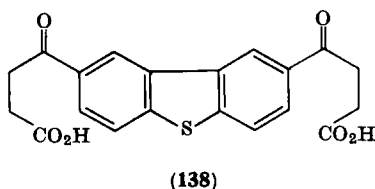
(**137a**) $R = H$
 (**137b**) $R = CH_3$

(61%). Huang-Minlon reduction of **135b** followed by cyclization yields **136b**.⁸⁹ The use of methylsuccinic anhydride in the above two reactions yields the keto acids **135c** and **135d**, respectively, reduction and cyclization of which yields **136c** and **136d**.⁴⁶¹ In each case substitution was shown to have occurred in the 2-position and cyclization in the 3-position of the dibenzothiophene nucleus by analysis of the 100 MHz NMR spectra

⁴⁷⁵ N. P. Buu-Hoi and P. Cagniant, *Chem. Ber.* **76**, 1269 (1943).

⁴⁷⁶ E. G. G. Werner, *Rec. Trav. Chim. Pays-Bas* **68**, 520 (1949).

of all the compounds prepared.⁴⁶¹ Using compounds of type **136** the C-10,11 sulfur isosteres (**137a**, **137b**) of cholanthrene and methylcholanthrene have been prepared⁴⁷⁷ along with a series of methyl-substituted analogs.⁴⁶¹ The position of R² in **135c** and **135d** was established by analysis of the NMR spectra of the derived methyl-substituted benzo[*b*]naphtho[2,3-*d*]thiophenes.⁴⁶¹ A separate study has been made of the acylation and diacylation of dibenzothiophene with succinic anhydride or the ester chloride of succinic acid.²³⁴ The use of either reagent gave good yields of **135a** and in each case the use of excess reagent gave 2,8-disubstitution, although the best yield of **138** was obtained by using the succinic ester followed by hydrolysis. Wolff-Kishner reduction of **138** gave the corresponding 2,8-bis(butyric acid). Wolff-Kishner reduction of **135a** gave 2-dibenzothiophenebutyric acid, which upon further treatment with succinic anhydride gave **136a** rather than the expected 8-substituted ketobutyric acid.



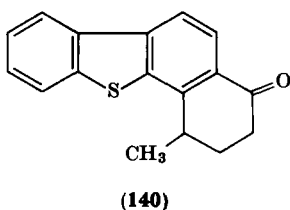
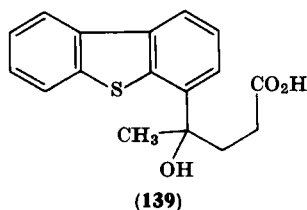
A low yield of γ -oxo-4-dibenzothiophenebutyric acid has been obtained by treatment of 4-lithiodibenzothiophene with succinic anhydride.⁴⁷⁸ Optimization of this reaction would enable the synthesis of γ -oxo-1- and γ -oxo-3-dibenzothiophenebutyric acid to be undertaken from the appropriate bromodibenzothiophenes.

An alternative route to dibenzothiophenebutyric acids has been developed⁴⁷⁸ involving reaction of 4-lithiodibenzothiophene with menthyl levulate,⁴⁷⁹ yielding, after ester hydrolysis, γ -hydroxy- γ -methyl-4-dibenzothiophenebutyric acid (**139**). The bulky menthyl group was employed to direct reaction to the ketone moiety of the levulate. Dehydration followed by catalytic hydrogenation yields γ -methyl-4-dibenzothiophenebutyric acid, Friedel-Crafts cyclization of which yielded the ketone (**140**).⁴⁷⁸

⁴⁷⁷ E. Campaigne, J. Ashby, and G. F. Bulbenko, *J. Heterocycl. Chem.* **7**, 1175 (1970).

⁴⁷⁸ W. Carruthers and H. N. M. Stewart, *J. Chem. Soc.*, 6221 (1956).

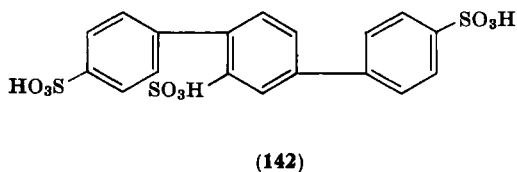
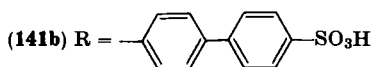
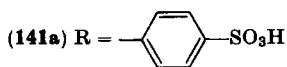
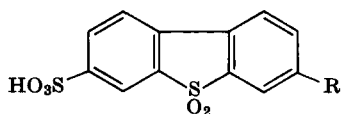
⁴⁷⁹ A. McKenzie, *J. Chem. Soc.*, 365 (1906).



3. Miscellaneous Acids

a. *Sulfonic Acids*. Many highly substituted derivatives of dibenzothiophene bearing sulfonic acid groups are described in the patent literature relating to optical brighteners and dyestuffs; however, the structures of these compounds are very rarely established; they are dealt with briefly in Section VI, E, 2. The sodium salts of sulfonated derivatives of dibenzothiophene 5,5-dioxide are also used in the preparation of lustrous nickel deposits.^{480, 480a, 481}

The 3,7-disulfonyl chloride of dibenzothiophene 5,5-dioxide has been isolated from the reaction of biphenyl with chlorosulfonic acid. The reaction proceeds via the 2,4,4'-trisulfonyl chloride of biphenyl.⁴⁸² This reaction has now been extended to give sulfonic acid derivatives of 3-phenyl- and 3-biphenyldibenzothiophene 5,5-dioxide. Treatment of *p*-terphenyl with oleum or chlorosulfonic acid at 100° yields (141a) (46%), and similarly *p*-quaterphenyl yields 141b (47%).⁴⁸³ A later



⁴⁸⁰ F. Passal and W. R. Dotey, U.S. Patent 3,245,887 (1966); *Chem. Abstr.* **65**, 8356 (1966).

^{480a} F. Passal and J. A. Hartman, U.S. Patent 3,041,255 (1962); *Chem. Abstr.* **57**, 13544 (1962).

⁴⁸¹ F. Passal, British Patent 1,138,262 (1968); *Chem. Abstr.* **70**, 83703 (1969).

⁴⁸² J. Pollak, M. Heimberg-Krauss, E. Katscher, and O. Lustig, *Monatsh. Chem.* **55**, 358 (1930).

⁴⁸³ J. A. Van Allan, *J. Org. Chem.* **21**, 1152 (1956).

publication included the isolation of the trisodium salt of *p*-terphenyl-2,4',4''-trisulfonic acid (**142**), a probable intermediate in the terphenyl synthesis.⁴⁸⁴ This observation, coupled with the fact that sulfonation of *p*-terphenyl under yet milder conditions produces 4,4''-*p*-terphenyl-disulfonic acid,⁴⁸⁵ confirms the positions of the sulfonic acid groups in **141a** and **141b**. Compounds of the general type **141** have been patented as photographic emulsion supersensitizers.^{440, 486}

The kinetics of hydrolysis of the sulfone of 3,7-dibenzothiophendi-sulfonyl chloride have been investigated in a 70% dioxane-water mixture. Hydrolysis rates were measured both conductometrically and titrimetrically.⁴⁸⁷

b. *Boronic Acids*. 2-Dibenzothiopheneboronic acid has been prepared by the action of triisopropyl borate on 2-lithiodibenzothiophene at -60° , followed by hydrolysis (22%).³⁵¹ Similarly, treatment of 4-lithiodibenzothiophene with tri-*n*-butyl borate yielded the 4-boronic acid after hydrolysis (32%). The 4-boronic acid melted at 339° , infrared spectroscopy indicating that the material present at the fusion point was in fact an anhydride. A low-yield synthesis (4%) of the 4-boronic acid employing methyl borate has also been described which quotes its melting point as greater than 360° .⁴⁸⁸

H. METALLIC DERIVATIVES

1. *Lithio and Other Metallic Derivatives*

During the period covered by this review the preparation of most of the sets of four isomeric monosubstituted dibenzothiophenes have been completed. The successful synthesis of the 1-, 3-, or 4-substituted isomers is due largely to the synthesis of the four monolithiodibenzothiophenes by several groups of workers. Despite the success of this work which is due mainly to the established versatility of lithium reagents, the need exists for a separate study of the optimum conditions for the

⁴⁸⁴ J. E. Jones, J. Spence, and J. A. Van Allan, U.S. Patent 2,937,089 (1960); *Chem. Abstr.* **55**, 19950 (1961).

⁴⁸⁵ C. Wulff and E. Roell, U.S. Patent 2,004,546 (1935); *Chem. Abstr.* **29**, 5282 (1935).

⁴⁸⁶ Kodak Soc. anon., Belgian Patent 556,149 (1957); *Chem. Abstr.* **54**, 130 (1960).

⁴⁸⁷ R. V. Vizgert, I. E. Kachanko, and V. F. Yavorovskaya, *Reakts. Sposobnost Org. Soedin.* **3**, 16 (1966); *Chem. Abstr.* **68**, 77368 (1968).

⁴⁸⁸ J. Yates and R. S. Airs, British Patent 814,647 (1959); *Chem. Abstr.* **54**, 8852 (1960).

⁴⁸⁹ R. H. Meen and H. Gilman, *J. Org. Chem.* **20**, 73 (1955).

formation and reaction of each lithio derivative. Yields are generally good but could probably be substantially increased by systematic attention to solvent, reaction temperatures, etc.

The formation of 4-lithiodibenzothiophene from dibenzothiophene and butyllithium has been dealt with in an earlier review;¹ however, several references to its chemistry have since appeared^{89, 104, 124, 146, 230, 231, 478, 489, 490} including an important study of the optimum conditions for the formation of this compound.⁴⁹¹ In this study the direct lithiation of dibenzothiophene was accomplished with methyl, *n*-butyl, and phenyllithium in various solvents and at varied temperatures, each reaction being quenched with carbon dioxide and the yield of 4-dibenzothiophenecarboxylic acid being taken as a measure of the overall efficiency of the reaction. From this work, the results of which are shown in Table IV, it is clear that mixed tetrahydrofuran-diethyl ether is the

TABLE IV
DIRECT FORMATION OF 4-LITHIODIBENZOTHIOPHENE
FROM DIBENZOTHIOPHENE^a

Solvent	RLi-Solvent	Addition conditions	Reaction conditions	Yield (%) ^b	
				Crude	Pure
Ether	CH ₃ Li-Ether	Room temp.	Room temp., 5.5 hr	Trace	—
THF	CH ₃ Li-Ether	Room temp.	Room temp., 5.5 hr	12.0	5.0
THF	CH ₃ Li-THF	Ice bath	Room temp., 5 hr	16.0	12.2
Ether	<i>n</i> -C ₄ H ₉ Li-Ether	Ice bath	Room temp., 5 hr	30.7	24.8
THF	<i>n</i> -C ₄ H ₉ Li-Ether	Ice bath	Room temp., 5 hr	90.0	60.0
THF	<i>n</i> -C ₄ H ₉ Li-Ether	- 30°	- 30°, 5 hr	12.2	10.1
THF	<i>n</i> -C ₄ H ₉ Li-THF	- 30°	- 30°, 5 hr	48.5	41.0
Ether	C ₆ H ₅ Li-Ether	Slight cooling	Room temp., 5 hr	1	—

^a From Gilman and Gray.⁴⁹¹ Reprinted from *J. Organ. Chem.* **23**, 1476 (1958), Copyright 1958 by the American Chemical Society. Reprinted by permission of the copyright owners.

^b Represents yield of derived 4-dibenzothiophenecarboxylic acid.

solvent of choice and 0° the optimum reaction temperature. Despite the clear-cut nature of these results, diethyl ether is still used by most workers, with, presumably, a consequent reduction in yields.

⁴⁹⁰ W. A. Hewett, J. D. Michaelsen, and J. F. Schimscheimer, U.S. Patent 3,294,763 (1966); *Chem. Abstr.* **66**, 38327 (1967).

⁴⁹¹ H. Gilman and S. Gray, *J. Org. Chem.* **23**, 1476 (1958).

The formation of 1-lithio-,^{104, 230, 231, 351} 2-lithio-,^{85, 104, 230, 231, 351, 489} and 3-lithiodibenzothiophene^{85, 104, 230, 231, 351} has been achieved by translithiation of the appropriate bromodibenzothiophene (Section VI, C, 3) with butyllithium. Higher yields of derivatives are obtained from 2-lithiodibenzothiophene by conducting the reactions at 0°⁸⁵ rather than at room temperature.³⁵¹ The comparatively low yield of compounds derived from 3-lithiodibenzothiophene at 0°⁸⁵ may indicate that even lower reaction temperatures are required for this particular isomer, reduced yields probably being due to ortho-translithiation to the thermally stable 4-lithiodibenzothiophene (cf. the instability of 3-lithio-benzo[*b*]thiophene at 0°⁶⁶). Both 2-lithio- and 3-lithio-4-methyldibenzothiophene have been prepared from the respective bromo compound,⁸⁹ and a similar synthesis of 1-lithio-4-methoxydibenzothiophene has been described.⁹⁰

Both 2,8-dilithio-^{76, 85, 351, 357} and 3,7-dilithiodibenzothiophene⁷⁶ have been obtained from the corresponding dibromides and in the former case it has been demonstrated that higher yields of derived product are obtained at 0°⁷⁶ rather than at room temperature.³⁵¹ Attempts to directly dilithiate dibenzothiophene with an excess of butyllithium have been largely unsuccessful. Termination of the reaction with carbon dioxide gave the 4-acid as sole product;⁴⁹² however, upon termination with dimethyl sulfate⁷⁶ a 15% yield of 4,6-dimethyldibenzothiophene was obtained along with material said to be 4-methyldibenzothiophene (Section VI, A, 2). Reaction of dibenzothiophene with excess butyllithium followed by hydrolysis with deuterium oxide gave a mixture which mass spectrometry showed to contain 68% monodeuterio- and 22% di-deuteriodibenzothiophene. The latter material was presumed to be 4,6-disubstituted.¹⁰³

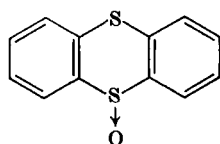
The transformation of lithio derivatives of dibenzothiophene into alkyl, alkenyl, hydroxyalkyl, formyl, acetyl, carboxylic acid, alkyl and arylsilyl, boronic acid, aryl and carbinol derivatives of dibenzothiophene is dealt with in the appropriate sections. In addition, the four monotritio derivatives of dibenzothiophene have been prepared from the corresponding lithio derivatives via hydrolysis with tritiated water (Section III, C, 2).¹⁰⁴

Metallation of dibenzothiophene 5-oxide with three equivalents of butyllithium followed by carbonation gave a mixture of 4-dibenzothiophene carboxylic acid (36%) and dibenzothiophene (10%).⁴⁹³ The reduction or even elimination of sulfoxide groups in the presence of

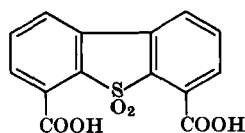
⁴⁹² H. Gilman and S. H. Eidt, *J. Amer. Chem. Soc.* **78**, 2633 (1956).

⁴⁹³ H. Gilman and D. S. Esmay, *J. Amer. Chem. Soc.* **74**, 266 (1952).

butyllithium is further illustrated by the treatment of thianthrene 5-oxide (**143**) with butyllithium, which afforded dibenzothiophene (50%),⁴⁹⁴ and by the reaction of the corresponding sulfone, thianthrene-5,5,10-trioxide, with butyllithium, which after carbonation gave a mixture of dibenzothiophene 5,5-dioxide (5%) and 2,2'-dicarboxy-diphenyl sulfone (26%).^{493, 494, 494a} The sulfone group is stable to butyl-



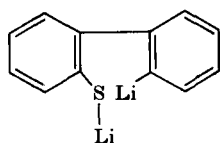
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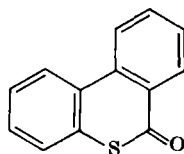
(144)

lithium and treatment of dibenzothiophene 5,5-dioxide with excess butyllithium, followed by carbonation, give a low yield of the corresponding 4,6-dicarboxylic acid (**144**).⁴⁹⁵

Treatment of dibenzothiophene with lithium metal in refluxing dioxane, gave, upon hydrolysis, a mixture of biphenyl (30%) and starting material (33%). Conducting the reaction under nitrogen followed by termination with carbon dioxide gave a similar mixture with the addition of *o*-mercaptobiphenyl (18%).²⁶⁷ The reaction was postulated to proceed via the dilithio derivative (**145**). The absence of carboxy incorporation in the latter reaction is in keeping with the destructive nature of refluxing dioxane on organometallic compounds. By conducting the reaction in THF at 25° a 48% yield of 3,4-benzothiocoumarin (**146**) was obtained along with a small amount of the disulfide of 2-mercapto-2'-carboxybiphenyl, both products being indicative of the intermediacy of **145**.⁴⁹⁶ Cleavage of dibenzothiophene with a 2:1 lithium-biphenyl adduct is reported to yield the thiocoumarin



(145)



(146)

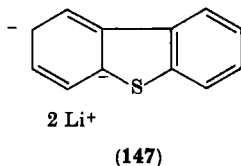
⁴⁹⁴ H. Gilman and D. R. Swayampati, *J. Amer. Chem. Soc.* **77**, 3387 (1955).

^{494a} H. Gilman and D. R. Swayampati, *J. Amer. Chem. Soc.* **79**, 208 (1957).

⁴⁹⁵ H. Gilman and D. L. Esmay, *J. Amer. Chem. Soc.* **75**, 278 (1953).

⁴⁹⁶ H. Gilman and J. J. Dietrich, *J. Org. Chem.* **22**, 851 (1957).

derivative (**146**) in high yield. The lithium-biphenyl adduct is thought to facilitate cleavage by providing a homogenous source of lithium for adduct formation by electron transfer under mild conditions, leading to the dianion (**147**), which after C-S bond cleavage yields the dilithio derivative (**145**).⁴⁹⁷ The 1-, 2-, 3- and 4-Grignard reagents of dibenzo-



thiophene along with the 2,8- and 1,4-di-Grignards have been prepared from the appropriate bromo compounds and magnesium and used in the preparation of mono- and diphenyl derivatives of dibenzothiophene (Section VI, B, 1).^{146, 357}

Phenylcalcium iodide metallates dibenzothiophene in the 3-position;¹ however, it has no effect on the corresponding sulfone.⁴⁹⁸ Mercuration of dibenzothiophene has been accomplished by adding mercuric acetate to a melt of dibenzothiophene, but the position of mercuration was not established.¹ Mercuric nitrate or bisulfite give no identifiable products.⁴⁹⁸ An unsuccessful attempt to metallate dibenzothiophene with cross-linked poly(*p*-lithiostyrene) in ether has been recorded.⁴⁹⁹

Dibenzothiophene 5-oxide reacts with triaryltin chlorides to give complexes which show bacteriostatic and fungistatic properties,⁵⁰⁰ and a chromium tricarbonyl complex of dibenzothiophene has been described.⁹⁷

2. Silyl Derivatives

The synthesis of 1-trimethylsilyldibenzothiophene^{230, 231, 351} completes the series of four, isomeric, trimethylsilyl derivatives.¹ All were synthesized by reacting the appropriate lithiodibenzothiophene with trimethylsilyl chloride under reflux, yields being in excess of 50%. The rates of cleavage of these compounds have been measured spectrophotometrically at 50° using a mixture of methanol and aqueous perchloric acid and comparisons made with the rates of protodesilylation

⁴⁹⁷ J. J. Eisch, *J. Org. Chem.* **28**, 707 (1963).

⁴⁹⁸ J. W. Morton, *Iowa State Coll. J. Sci.* **28**, 367 (1954); *Chem. Abstr.* **49**, 8163 (1955).

⁴⁹⁹ D. Braun and E. Seelig, *Chem. Ber.* **97**, 3098 (1964).

⁵⁰⁰ C. H. Boehringer Sohn., German Patent 1,215,709 (1966); *Chem. Abstr.* **65**, 5489 (1966); *Neth. Application* 6,510,858 (1966); *Chem. Abstr.* **65**, 17004 (1966).

of 2- and 4-trimethylsilyldiphenyl sulfide.^{230, 231} The results of this study are discussed in Section III, C, 2.

Treatment of 2-bromodibenzothiophene in ether with triphenylsilylpotassium gave 2-triphenylsilyldibenzothiophene. This material was also formed by the reaction of 2-lithiodibenzothiophene with triphenylsilyl chloride, although when applied to the synthesis of the 4-triphenylsilyl compound this method gave a poor yield (11%).⁴⁸⁹ Unlike the corresponding trimethylsilyl compounds, 2- and 4-triphenylsilyldibenzothiophene were stable to refluxing acetic-hydrochloric acid mixtures. The 2-isomer was also stable to hot ethanolic potassium hydroxide, although the 4-isomer under these conditions underwent a 44% conversion to dibenzothiophene.⁴⁸⁹ The greater stability of the $(\text{C}_6\text{H}_5)_3\text{Si}-\text{C}$ bond as compared to the $(\text{CH}_3)_3\text{Si}-\text{C}$ bond has been observed in other series⁵⁰¹ and can be explained by resonance stabilization.

In all of the above preparations the lithium exchange step was conducted in ether. The use of a mixed ether-THF solvent system would probably improve the yields (Section VI, H, 1).

VII. Polymers of Dibenzothiophenes

A. ADDITION TYPE

Dibenzothiophene derivatives have been used as co-catalysts in the addition polymerization of vinyl and diene monomers.^{502, 503} Dibenzothiophene itself, in conjunction with vanadium oxychloride, is effective in initiating the polymerization of isobutylene,^{504, 505} although when incorporated⁵⁰⁶ in a Ziegler catalyst system, competition between donor and monomer for the most electrophilic sites results in deactivation of the catalyst. Despite the fact that 2-vinyl-^{1, 407, 464, 507-509} and 4-vinyldibenzothiophene^{124, 490} readily undergo thermal polymerization,

⁵⁰¹ H. Gilman and F. J. Marshal, *J. Amer. Chem. Soc.* **71**, 2066 (1949).

⁵⁰² O. W. Burke, Jr., British Patent 873,656 (1957); *Chem. Abstr.* **56**, 8927 (1962).

⁵⁰³ O. W. Burke, Jr., British Patent 936,132 (1963); *Chem. Abstr.* **60**, 5661 (1964).

⁵⁰⁴ Teijin Ltd., French Patent 1,389,120 (1965); *Chem. Abstr.* **63**, 4415 (1965).

⁵⁰⁵ N. Yamada, K. Shimada, and T. Hayashi, *J. Polym. Sci., Part B* **4**, 477 (1966).

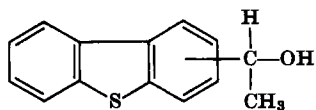
⁵⁰⁶ A. Schindler, *Makromol. Chem.* **105**, 204 (1967).

⁵⁰⁷ R. G. Flowers and L. W. Flowers, U.S. Patent 2,499,186 (1950); *Chem. Abstr.* **44**, 5393 (1950).

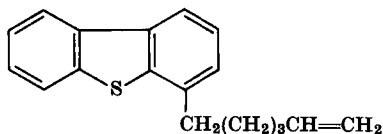
⁵⁰⁸ I. V. Andreeva and M. M. Koton, *Dokl. Akad. Nauk SSSR* **110**, 75 (1956); *Chem. Abstr.* **51**, 5039 (1957).

⁵⁰⁹ British Thompson Houston Co. Ltd., British Patent 661,503 (1951); *Chem. Abstr.* **46**, 5365 (1952).

they can be prepared as monomers in average yields of 50% by vapor-phase dehydration of the appropriate hydroxyethylthiophene (148) over alumina, provided a polymerization inhibitor is present.



(148)

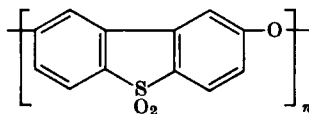


(149)

Polymerization of 4-vinyldibenzothiophene, using either thermal or free-radical initiation, gives a high yield of polymers softening at 250° ^{124, 490} while the use of a Ziegler catalyst gives a low yield of material softening at 150° .¹²⁴ The polymerization of 2-vinyldibenzothiophene within the range 35° to 120° alone, or with other vinyl compounds, gives polymers softening in the range 175° – 200° .^{464, 508–511} The kinetics of the polymerization of 2-vinyldibenzothiophene have been studied and the rate found to be much greater than for the polymerization of 2-vinylthiophene. This was attributed to the presence of condensed rings in the monomer, a generally observed accelerating factor.^{508, 511} The preparation of 4-(5'-hexenyl)dibenzothiophene (149) from 4-lithiodibenzothiophene and its polymerization have been reported.⁴⁹⁰ All of the above polymers are claimed as being useful as binders and coatings and have found special use as dielectrics in paper-insulated capacitors.^{490, 510, 511}

B. CONDENSATION TYPE

Self-condensation of the potassium salt of 2-hydroxy-8-bromodibenzothiophene 5,5-dioxide in dimethyl sulfone gives a thermoplastic polymer of unit structure 150.⁵¹²



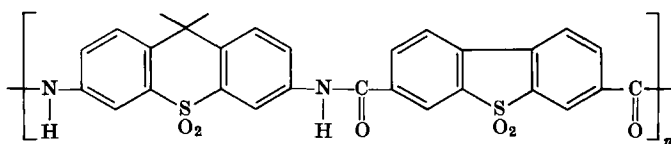
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⁵¹⁰ R. G. Flowers and L. W. Flowers, U.S. Patent 2,499,187 (1950); *Chem. Abstr.* **44**, 5642 (1950).

⁵¹¹ I. V. Andreeva and M. M. Koton, *Zh. Fiz. Khim.* **32**, 1847 (1958); *Chem. Abstr.* **53**, 4805 (1959).

⁵¹² V. J. Leslie, J. B. Rose, and A. B. Newton, German Patent 2,038,241 (1971); *Chem. Abstr.* **74**, 126508 (1971).

Heat-resistant condensation polymers, softening within the range 170°–400° and of molecular weights 800–2550, have been prepared by condensation of dibenzothiophene with a number of acid chlorides including terephthaloyl chloride.^{513, 514} The incorporation of 3,7-diaminodibenzothiophene 5,5-dioxide into polyamide or polyimide structures gives polymers of high heat and solvent stability.^{515–517} Film-forming, solvent-soluble polyamides are obtained by the condensation polymerization of the 3,7-diacid chloride of dibenzothiophene 5,5-dioxide with an aromatic diamine containing a bridging group, giving polymers of type **151**.⁵¹⁸ Condensation of diaminodibenzothio-



(151)

phenes such as 3,7-diaminodibenzothiophene-2,8-disulfonic acid, or its sulfone, with carbonyl chloride has enabled a series of polyureas of type **152** to be prepared, of molecular weight 14,000–440,000.^{519, 520} Condensation products of type **153**, formed from the reaction of 2,8-diaminodibenzothiophene or 3,7-diaminodibenzothiophene 5,5-dioxide with pyridine in the presence of cyanogen bromide, are useful as pigments and herbicides.^{512, 522} Cross-linked, heat-stable sealants and

⁵¹³ J. M. Lancaster, B. A. Wright, and W. W. Wright, *J. Appl. Polym. Sci.* **9**, 1955 (1965).

⁵¹⁴ A. Kutner and M. J. S. Dewar, British Patent 1,060,611 (1967); *Chem. Abstr.* **66**, 105,341 (1967).

⁵¹⁵ F. F. Holub and J. T. Hoback, German Patent 1,922,315 (1969); *Chem. Abstr.* **72**, 32895 (1970).

⁵¹⁶ F. F. Holub and J. T. Hoback, German Patent 1,922,339 (1970); *Chem. Abstr.* **72**, 79925 (1970).

⁵¹⁷ F. F. Holub and J. T. Hoback, French Patent 2,008,042 (1970); *Chem. Abstr.* **73**, 46209 (1970).

⁵¹⁸ H. E. Hinderer and R. W. Smith, U.S. Patent 3,467,623 (1969); *Chem. Abstr.* **71**, 114066 (1969).

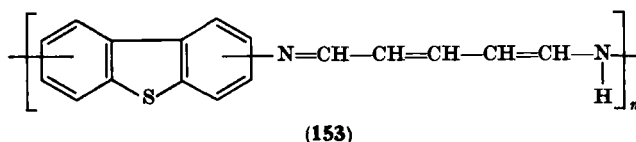
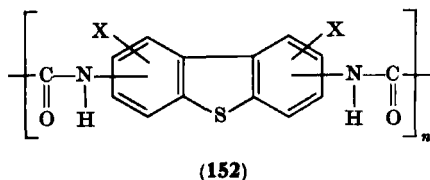
⁵¹⁹ R. Neher, Swiss Patent 322,061 (1957); *Chem. Abstr.* **52**, 3859 (1958).

⁵²⁰ R. Neher, U.S. Patent 2,833,744 (1958); *Chem. Abstr.* **52**, 13786 (1958).

⁵²¹ Laboratoires français de chimiothérapie, French Patent 978,499 (1951); *Chem. Abstr.* **48**, 2772 (1953).

⁵²² Laboratoires français de chimiothérapie, French Patent 978,500 (1951); *Chem. Abstr.* **48**, 2772 (1953).

insulation products of low molecular weight have been prepared by the condensation of dibenzothiophene and 2-phenyldibenzothiophene with α, α' -dichloro-*p*-xylene.^{523, 524} The synthesis of several dibenzothiophene formaldehyde copolymers has recently been described.⁵²⁵



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The early stages of preparation of this manuscript were carried out at the Department of Chemistry and Applied Chemistry, University of Salford, and we wish to thank Professor H. Suschitzky for his help during this period. We are also grateful for assistance afforded by Dr. S. McLintock and staff of Bradford University Library and the library staff of I.C.I. Pharmaceuticals Division.

⁵²³ Monsanto Chemicals Ltd., French Addition 83,559 (1964); *Chem. Abstr.* **62**, 13361 (1965).

⁵²⁴ L. N. Phillips, British Patent 1,024,222 (1966); *Chem. Abstr.* **64**, 19904 (1966).

⁵²⁵ E. Gipstein, A. C. Ouano, and W. A. Hewett, *Macromolecules* **5**, 249 (1972).

Cationic Polar Cycloaddition

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I. Introduction

The classical 4 + 2 Diels–Alder reaction involves the thermally allowed cycloaddition of an electron-rich (nucleophilic) diene $a=b-c=d$ with an electron-deficient (electrophilic) dienophile $e=f$. In the polar cycloaddition reactions considered here, the $a=b-c=d$ system bears a positive charge and is so obviously ill-suited for a nucleophilic role that the first examples¹ of polar cycloaddition appeared inexplicable in terms of cycloaddition theory then current. In 1962 Sauer and Wiest² demonstrated the existence of a “Diels–Alder reaction with inverse electron demand” in which the electronic roles of $a=b-c=d$ and $e=f$ are exchanged, with the former becoming the electrophile and the latter

¹ C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.* **80**, 933 (1958).

² J. Sauer and H. Wiest, *Angew. Chem.* **74**, 353 (1962).

the nucleophile. It remains to be demonstrated whether cycloadditions of the Sauer and Wiest type form an exact parallel with the classical Diels–Alder reaction, but in any case it must be recognized that the existence of an actual positive charge on the electrophilic species in cationic polar cycloaddition distinguishes it from these other types of cycloaddition, and make it, at best, a *limiting* case of the “Diels–Alder with inverse electron demand.”

In particular, the formal positive charge present in polar cycloaddition would be expected to influence the formation and geometry of intermediate charge-transfer complexes and the electrophilic character of the reaction with alkenes. As will be seen later, these effects result in important influences upon the regio- and stereochemistry as well as the concertedness³ of polar cycloaddition.

Professor Richard R. Schmidt⁴ appears to have been the first to recognize the existence of a variety of polar 1,4-cycloaddition reactions, the first to so designate them, and the first to attempt to create a unifying theory. For the purposes of the present review, the theory suffers chiefly from its inclusion of nonconjugated systems and from its failure to consider what is unquestionably the largest group of polar cycloadditions, those in which the electrophile is of the type $C=C-\overset{|}{N}^+=C$.^{4a}

II. Polar Cycloadditions in Which Cationic Aromatic Systems Act as Electrophiles

A. THE ACRIDIZINIUM ION AND ITS CONGENERS

Although it is possible to have a polar cycloaddition with a cation containing only carbon and hydrogen, the majority of those which have been found to undergo 1,4-cycloaddition are aromatic quaternary salts. The acridizinium cation (**1**) used in the first polar cycloaddition reaction of a quaternary salt¹ has been used in the largest number of polar cycloaddition studies to date. The acridizinium ion (**1**) is particularly suitable for such a study since it is easily prepared, is stable (permitting sealed

³ R. Gompper, *Angew. Chem., Intern. Ed. Engl.* **8**, 312 (1969).

⁴ R. R. Schmidt, *Tetrahedron Lett.*, 3443 (1968).

^{4a} *Note Added in Proof*: For a more adequate presentation of Dr. R. R. Schmidt's present views on the subject of polar cycloaddition, see *Angew. Chem., Int. Ed. Engl.* **12**, 212 (1973).

tube reactions at temperatures as high as 140°),⁵ and is sufficiently reactive to react with many poorly nucleophilic alkenes.¹

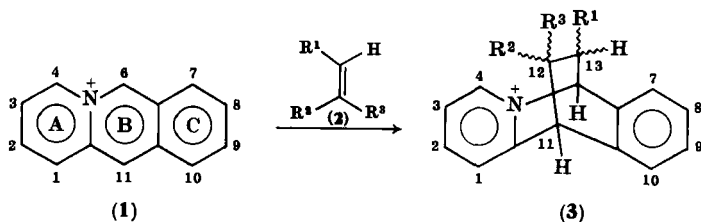


Table I records the results obtained in the preparation of 30 cycloaddition products from the acridizinium cation. As was demonstrated by Fields, Regan, and Dignan,⁶ even preparative experiments done at different temperatures and in different solvents are adequate to prove the inverse electron demand character of the reaction. Nucleophilic alkenes, like ketene diethyl acetal, reacted in minutes at room temperature while the strongly electrophilic alkene, tetracyanoethylene, failed to react under any conditions.

The yields of product isolated when para-substituted styrenes were allowed to react with the acridizinium ion (Table I) are not indicative of the rates of reaction. In an experiment patterned after that used by Sauer and Wiest² in the first demonstration of the existence of cycloaddition with inverse electron demand, it was shown⁷ that the relative rates of addition of para-substituted styrenes to the acridizinium nucleus were as follows: CH₃O, 4.3; CH₃, 1.7; H, 1.0; NO₂, 0.34; or in the order expected from the nucleophilicity of the styrenes.

Fields *et al.*⁶ showed that a variety of unsymmetrical alkenes added regiospecifically to the acridizinium nucleus and pointed out that the great majority of cases could be rationalized by the assumption that the more negatively polarized end of the alkene was preferentially attracted toward position 6, the previously demonstrated¹¹ center for nucleophilic attack on the acridizinium ring. At the same time they reported that the addition of acrylonitrile to yield a 12- rather than a 13-cyano adduct is the reverse of what would be expected from the polarization of the acrylonitrile molecule. Possible explanations for this "exception" are offered in Section V.

Elucidation of the structure of the cycloadducts (3) by nuclear magnetic resonance is simplified by the strong deshielding effect of the positively

⁵ W. S. Burnham and C. K. Bradsher, *J. Org. Chem.* **37**, 355 (1972).

⁶ D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.* **33**, 390 (1968).

⁷ C. K. Bradsher and J. A. Stone, *J. Org. Chem.* **33**, 519 (1968).

TABLE I
ADDITION OF ALKENES (2) TO THE ACRIDIZINIUM ION (1)

Structure 2			Temp. (0°C)	Time (hr)	Yield (%)	Stereo- chem. at 12, 13 ^a
R ¹	R ²	R ³				
H	H	H	70	18	93 ⁶	—
H	Et	H	70	66	66 ⁶	U
H	CH=CH ₂	H	70	18	93 ⁶	U
H	CH ₂ OH	H	100	18	77 ⁶	U
H	CN	H	70	48	68 ⁶	U
H	Ph	H	100	2.5	93 ⁶	U
H	<i>p</i> -CH ₃ C ₆ H ₄	H	100	10	78 ⁷	U
H	<i>p</i> -CH ₃ OC ₆ H ₄	H	100	10	50 ⁷	U
H	<i>p</i> -NO ₂ C ₆ H ₄	H	100	10	60 ⁷	U
H	9-Carbazyl	H	20	15	68 ⁸	U
H	1-Pyrr ^b	H	20	12	50 ⁸	U
H	OEt	H	20	72	91 ⁸	syn ⁹
H	OBu	H	82	12	64 ⁸	U
H	OAc	H	65	72	89 ⁸	U
Cl	H	Cl	130	90	46 ⁸	U
CO—O—CO	CO	H	100	13	87 ¹	anti ⁷

CO—N(Ph)—CO	H	100	20	95	anti ¹⁰	
CO—N(<i>p</i> -CH ₃ C ₆ H ₄)—CO	H	100	20	85	anti ¹⁰	
CO—N(<i>p</i> -ClC ₆ H ₄)—CO	H	100	20	90	anti ¹⁰	
CO—N(<i>p</i> -CH ₃ OC ₆ H ₄)—CO	H	100	20	90	anti ¹⁰	
CO—N(<i>p</i> -(CH ₃) ₃ ⁺ NC ₆ H ₄)—CO	H	100	20	60	anti ¹⁰	
COOEt	H	COOEt	105	10	54 ¹	anti, syn ⁷
COOMe	H	COOMe	100	24	96	anti, syn ⁷
COOMe	COOMe	H	160	0.3	44	syn ¹⁰
Ph	H	N(Et) ₂	25	0.1	91 ⁶	U
H	Ph	N-morph ^c	25	0.1	84 ⁶	U
H	Me	Prop ^d	100	1.5	66 ⁶	U
H	OEt	OEt	25	0.1	92 ⁶	—
Me	OEt	OEt	25	0.1	93 ⁶	U
Br	OEt	OEt	70	2	100 ⁶	U
Ph	OEt	OEt	70	0.1	100 ⁶	U

^a U, unknown; anti or syn (with respect to the phenylene ring).

^b 1-Pyrrolidin-2-one.

^c *N*-morpholinyl.

^d Isopropenyl.

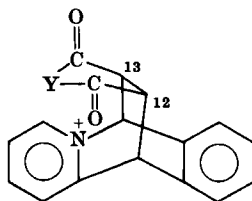
⁸ W. S. Burnham and C. K. Bradsher, *J. Org. Chem.* **37**, 355 (1972).

⁹ F. H. Day, Ph.D. Dissertation, Duke University, Durham, North Carolina, 1972.

¹⁰ C. K. Bradsher and D. J. Harvan, *J. Org. Chem.* **36**, 3778 (1971).

charged nitrogen atom. Fields *et al.*⁶ have recorded that the proton at C-6 (adjacent to N) appears in the range $\delta 6.63 \pm 0.14$ while that at C-11 appears at $\delta 5.49 \pm 0.21$. They made use of the multiplicities of these signals to determine the regiochemistry of cycloadducts obtained from unsymmetrically substituted alkenes. Although Fields and his associates⁶ reported that there was NMR evidence for the existence of stereoisomerism, no pure stereoisomer was identified.

In the first cycloaddition reaction of the acridizinium ion,¹ that with maleic anhydride, it had been observed that addition had occurred with great stereoselectivity, although it was not ascertained whether the product (4) was syn or anti with respect to the benzenoid ring. It was later demonstrated⁷ by use of NMR and IR evidence (derived from the



(4) Y = O

(5) Y = *p*-XC₆H₄N

[X = H, CH₃, Cl, OCH₃, N⁺(CH₃)₃]

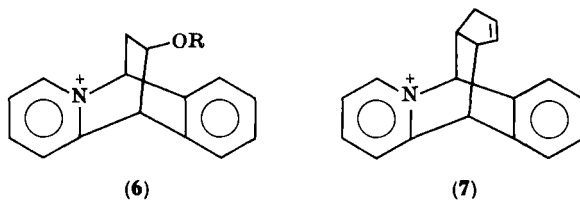
dimethyl ester obtained by opening the anhydride ring) that in 4 the anhydride ring is anti with respect to the phenylene ring. Similar stereoselectivity was shown in the reaction of *N*-arylmaleimides¹⁰ with the acridizinium ion, the adducts (5) being invariably anti. The orientation was not altered by the introduction of various substituents into the para position of the *N*-phenyl group, for even when the substituent was the trimethylammonium group, the adduct [5, X = N(CH₃)₃⁺] was anti. The orientation may be explained by a charge-transfer complex caused by the attraction of the positive charge by the unshared valence electrons of the heteroatom of the maleic anhydride or imide ring.

Based on NMR evidence as well as analogy with results obtained with isoquinolinium salts,¹² it appears certain that adducts (6) obtained from vinyl ethers invariably have the alkoxy group turned away from the quaternary nitrogen or, in other words, are syn with respect to the

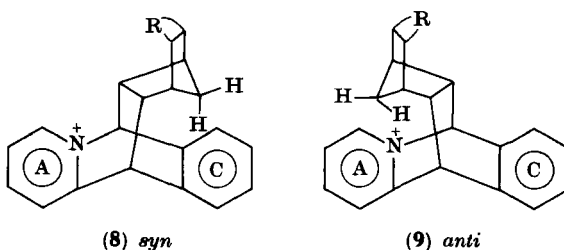
¹¹ C. K. Bradsher and J. H. Jones, *J. Amer. Chem. Soc.* **81**, 1938 (1959).

¹² C. K. Bradsher, F. H. Day, A. T. McPhail, and P. Wong, *Tetrahedron Lett.*, 4205 (1971).

phenylene ring.^{9,13} On the same type of evidence,¹³ the addition of cyclopentadiene to the acridizinium ion⁶ must also be stereospecific affording the syn adduct (7). As will be discussed more fully later, the stereospecificity is believed to arise because these orientations minimize repulsion of like charges in the transition state.



Not shown in Table I are several adducts obtained by cycloaddition of the acridizinium ion with 5,6-endo-substituted norbornene derivatives.¹⁴ These adducts each have two (unequally shielded) methylene hydrogen atoms which make simple the NMR analysis of mixtures of syn (8) and anti (9). When the 5,6-endo chain (R) was of the type



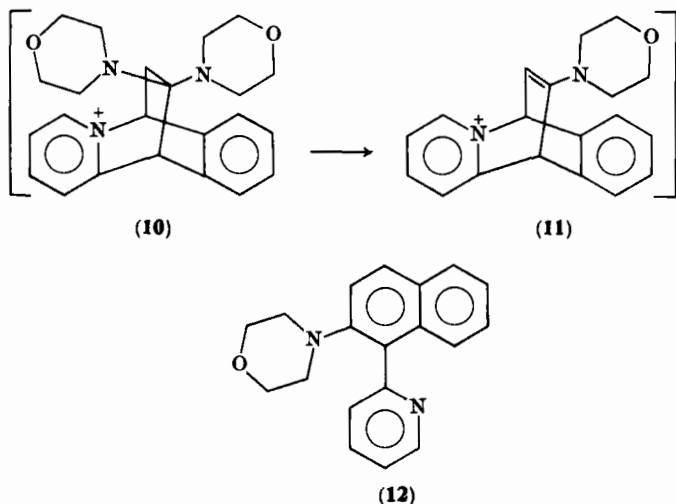
—C— \ddot{X} —C— (where X was an atom having an unshared pair of electrons) there was no evidence of the formation of any but the syn isomer, while in the absence of any 5,6-chain the syn:anti ratio was approximately 60:40.

Fields *et al.*⁶ found one example of an alkene, 1,1-dimorpholinoethylene, which did not give the expected cycloaddition product, the 12,12-dimorpholino-6,11-dihydro-6,11-ethanoacridizinium ion (10). They conjectured that the 1-(2-pyridyl)-2-morpholinonaphthalene (12) isolated had been formed via the expected adduct (10) which had undergone loss of morpholine to form the enamine (11) which could undergo ring opening (via a retro-quaternization reaction) followed by loss of a proton to yield (12).

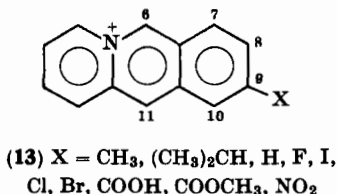
¹³ C. K. Bradsher, F. H. Day, A. T. McPhail, and P. Wong, *Chem. Commun.*, 156 (1973).

¹⁴ M. E. Parham, M. G. Frazer, and C. K. Bradsher, *J. Org. Chem.* **37**, 358 (1972).

A number of cycloadducts have been prepared from substituted acridizinium salts. Bradsher and Stone¹⁵ studied the rate of addition of styrene to acridizinium salts having methyl groups at the meso (6,11) positions.



The importance of the intensity of positive charge at position 6 was illustrated by the study¹⁶ of the effect of 9-substitution (see 13) on the rate of cycloaddition with styrene. The results will be discussed in Section V.



Significant synthetic application of the reaction products of the acridizinium ion with alkenes has been made by Fields *et al.*¹⁷⁻²¹ Although properly these new transformations lie outside the scope of this review,

¹⁵ C. K. Bradsher and J. A. Stone, *J. Org. Chem.* **34**, 1700 (1969).

¹⁶ I. J. Westerman and C. K. Bradsher, *J. Org. Chem.* **36**, 969 (1971).

¹⁷ D. L. Fields and T. H. Regan, *J. Org. Chem.* **35**, 1870 (1970).

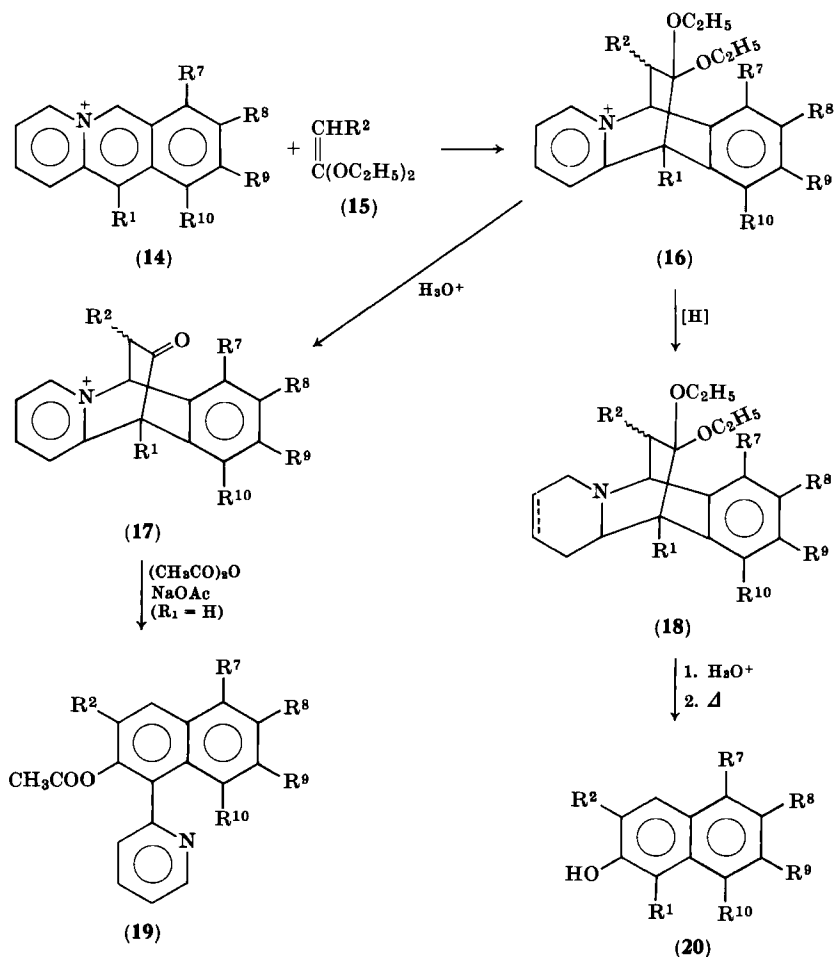
¹⁸ D. L. Fields and T. H. Regan, *J. Org. Chem.* **36**, 2986 (1971).

¹⁹ D. L. Fields and T. H. Regan, *J. Org. Chem.* **36**, 2991 (1971).

²⁰ D. L. Fields, T. H. Regan, and R. E. Graves, *J. Org. Chem.* **36**, 2995 (1971).

²¹ D. L. Fields, *J. Org. Chem.* **36**, 3002 (1971).

they serve to illustrate the importance of polar cycloaddition. The cycloaddition product **16** formed by reaction of a substituted acridizinium salt **14** with a ketene acetal **15** undergoes acid-catalyzed hydrolysis at room temperature to yield the cyclic ketone **17** which, when heated



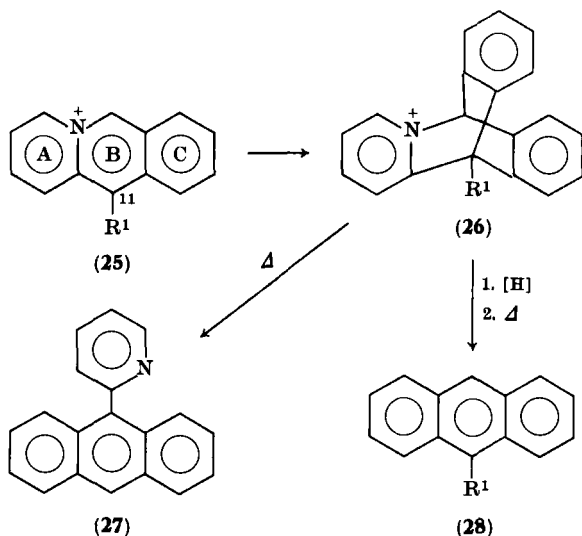
with acetic anhydride and sodium acetate, affords the acetate **19** of a 1-(2-pyridyl)-2-naphthol derivative.

If, prior to treatment with acid, the cycloadduct is reduced (perhaps incompletely) the product **18** when hydrolyzed and heated, loses unidentified amine products affording the nitrogen-free naphthol **20**.

Although dimethyl acetylenedicarboxylate was reported⁶ earlier not to undergo cycloaddition with the acridizinium ion, it was later

found⁸ that cycloaddition could be achieved by using a sealed tube at 135°–140°. As may be seen in Table II etheno-bridged adducts (23) are isolated only when there is an alkyl or aryl group present at position 11 of the acridizinium cation. If no such substituent is present, the adduct undergoes a dequaternization reaction and loses the proton at position 11, affording a 1-(2-pyridyl)naphthalene derivative (24). This ring-opening reaction closely resembles the transformation of ketene acetal cycloadducts (16) to 1-(2-pyridyl)-2-naphthol derivatives (19) observed earlier by Fields *et al.*¹⁷

Another important observation by Fields *et al.*²⁰ was that the acridizinium ion (25) will undergo cycloaddition with benzyne, affording



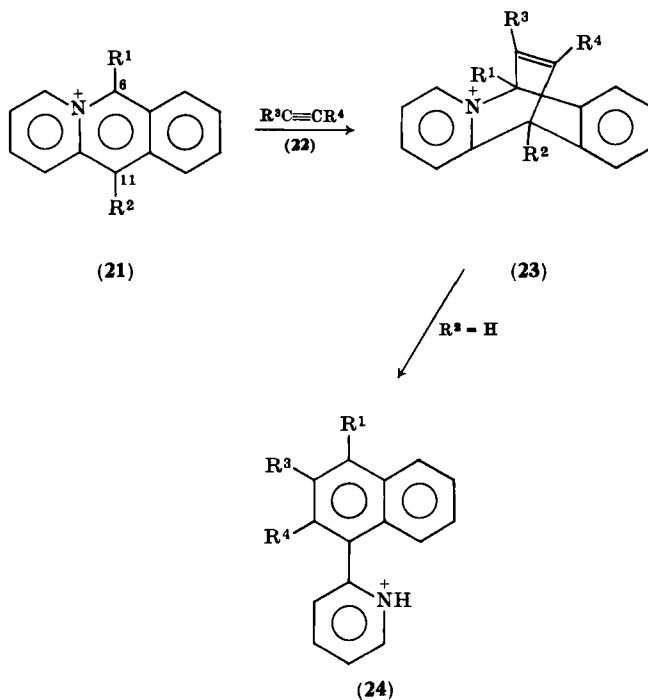
azoniatriptycenes (26) in good yield. The presence of a phenyl group at position 11 (25, R₁ = Ph) did not interfere with the cycloaddition nor did a variety of substituents on ring C.

This first example of the participation of benzyne in a polar cycloaddition gains added importance from two ring-opening reactions which Fields *et al.* have carried out on the adducts (26). The first²⁰ is simply thermolysis to afford 9-(2-pyridyl)-anthracene derivatives (27), while the second²¹ involves thermolysis of the reduction product of 26, affording anthracene derivatives (28) in excellent yields.

Fields *et al.*⁶ have pointed out that the differences observed between the rate of cycloaddition of ketene acetal with the acridizinium ion and that of various acridizinium benzologs qualitatively parallels those which are encountered when the rate of cycloaddition of maleic anhydride with

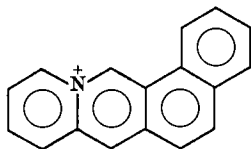
TABLE II

CYCLOADDITION REACTIONS OF ACRIDIZINIUM DERIVATIVES (21) WITH ACETYLENES (22)

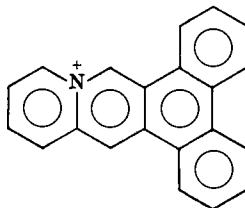


R ¹	R ²	R ³	R ⁴	Time (hr)	Product	Yield (%)
R ² = Alkyl or aryl						
H	Me	H	Ph	0.75	23	62
H	Ph	H	Ph	0.75	23	50
H	Me	COOMe	COOMe	0.1	23	93
H	Ph	COOMe	COOMe	1.75	23	30
H	Me	Ph	Ph	40	23	85
H	Ph	Ph	Ph	239	23	40
R ² = H						
H	H	H	Ph	3.0	24	70
Me	H	H	Ph	8.0	24	80
H	H	H	<i>n</i> -Bu	12	24	78
H	H	Ph	Ph	250	24	30

anthracene is compared with that of anthracene's benzologs. In a specific example, the fact that benz[*a*]anthracene is less reactive toward maleic anhydride than is anthracene yet more reactive than dibenz[*a,c*]anthracene²² leads one to predict (correctly) that the benz[*h*]acridizinium ion²³ (29) will react with ketene acetal more slowly than does the acridi-



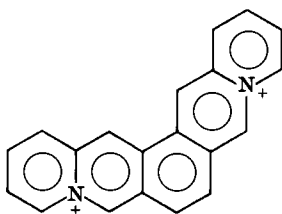
(29)



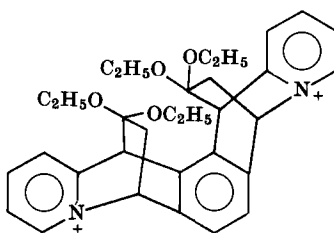
(30)

zinium ion, but more rapidly than does the dibenz[*h,j*]acridizinium system (30). Satisfactory yields were reported with these and other polycyclic derivatives.

An important extension^{6,19} of the ketene acetal cycloaddition involved the diazoniapentaphenes.²⁴ An example is the conversion of 4a,8a-bis(azonia)pentaphene (31) to a mixture of two diadducts of which 32 represents the stereoisomer formed by addition of both mole-



(31)



(32)

cules of the acetal to the same side. The stereoisomers were not separated but used directly in further transformations.^{20, 21} Also benzyne formed diadducts which underwent the transformations described earlier.^{20, 21}

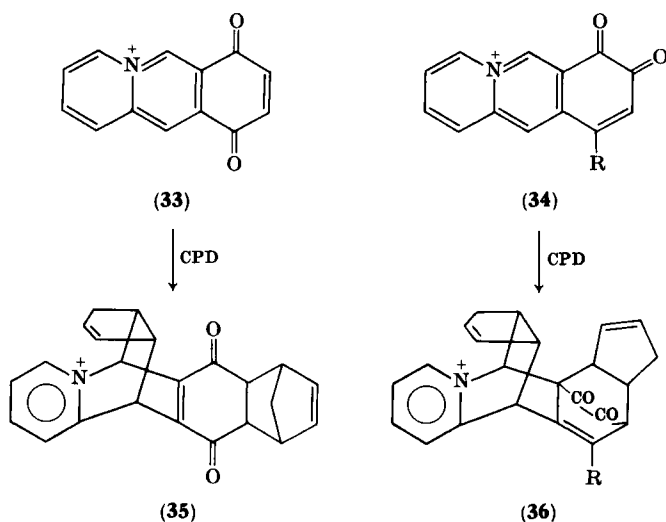
Some insight into the cycloaddition reactions of the acridizinium ion is provided by studying the effect of the change in nature of ring C. Fields

²² E. Clar, "Polycyclic Hydrocarbons," Vol. I, p. 311. Academic Press, New York, 1964.

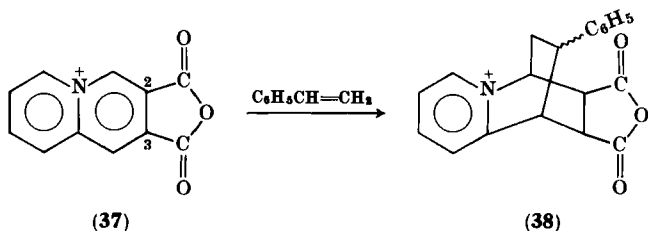
²³ C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.* **78**, 2459 (1956).

²⁴ C. K. Bradsher and J. C. Parham, *J. Org. Chem.* **29**, 856 (1964).

and Miller²⁵ showed that cycloaddition occurred across the meso positions of quinone derivatives **33** and **34** with excess cyclopentadiene, but in both instances, there was a second addition involving the quinone ring yielding what was believed to be **35** and **36**.



The replacement of ring C by a cyclic anhydride ring could be looked upon either as elimination of ring C or replacement of the ring by a heterocyclic anhydride ring. In any case, Fields *et al.*⁶ showed that quinolizinium 2,3-dicarboxylic acid anhydride (**37**) underwent cycloaddition reactions with either cyclopentadiene or styrene to afford the expected products (e.g., **38**). The 2,3-dimethylquinolizinium ion did not undergo cycloaddition even with the more reactive ketene diethylacetal.

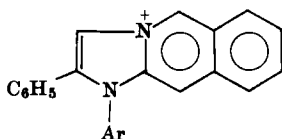


When ring A was replaced by an imidazo ring, it was found²⁰ that the new system (**39**) was less reactive than acridizinium (probably due to

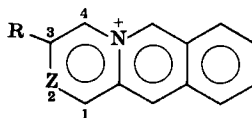
²⁵ D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.* **7**, 91 (1970).

²⁶ C. K. Bradsher, M. G. Frazer, and W. S. Burnham, *J. Heterocycl. Chem.* **9**, 177 (1972).

greater delocalization of the positive charge), but adducts were obtained with cyclopentadiene and *N*-vinylcarbazole. When ring A of the acridizinium cation was replaced by a pyrazine ring (as the *N*-oxide), the resulting system (40) showed an understandable enhancement of the



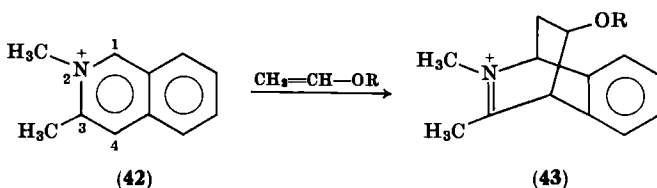
(39)

(40) Z = NO, R = H, CH₃, C₆H₅(41) Z = N, R = C₆H₅

rate of cycloaddition. Adducts were obtained with cyclopentadiene, *N*-vinylcarbazole, and ethyl vinyl ether. Only one of the oxides (40, R = Ph) was reduced to remove the oxide function at position 2. The resulting aza compound (41) underwent the cycloaddition reaction at a rate significantly slower than did the comparable oxide (40, R = Ph)

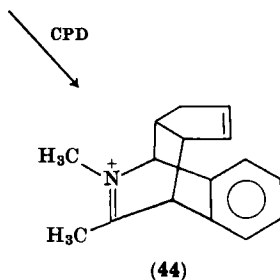
B. THE ISOQUINOLINIUM ION

The most recent extension of the 4 + 2 cycloaddition to aromatic quaternary salts has been carried out with isoquinolinium salts (42), in effect, dispensing with ring A of the acridizinium ion. Although there was an earlier claim²⁷ that the addition of an ynamine to 2-methylisoquinolinium iodide led to a 2:1 adduct, the assigned structure



(42)

(43)



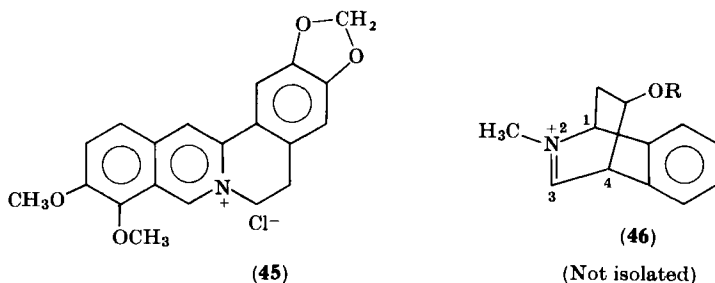
(44)

²⁷ R. Fuks, G. S. D. King, and H. G. Viehe, *Angew. Chem. Int. Ed. Engl.* **8**, 675 (1969).

was explained as a $2 + 2$ cycloaddition, followed by ring expansion and $4 + 2$ cycloaddition.

The addition of vinyl ethers or cyclopentadiene occurs not only in a $1 : 1$ manner affording $4 + 2$ cycloaddition products **43**²⁸ and **44**,¹³ but the reaction is also regio- and stereospecific,^{29, 13} as demonstrated by NMR and single-crystal X-ray analysis. The probable origin of these specific orientations will be discussed in Part V.

Berberinium chloride (**45**) also undergoes stereospecific cycloaddition reactions with vinyl ethers²⁸ or cyclopentadiene.⁹



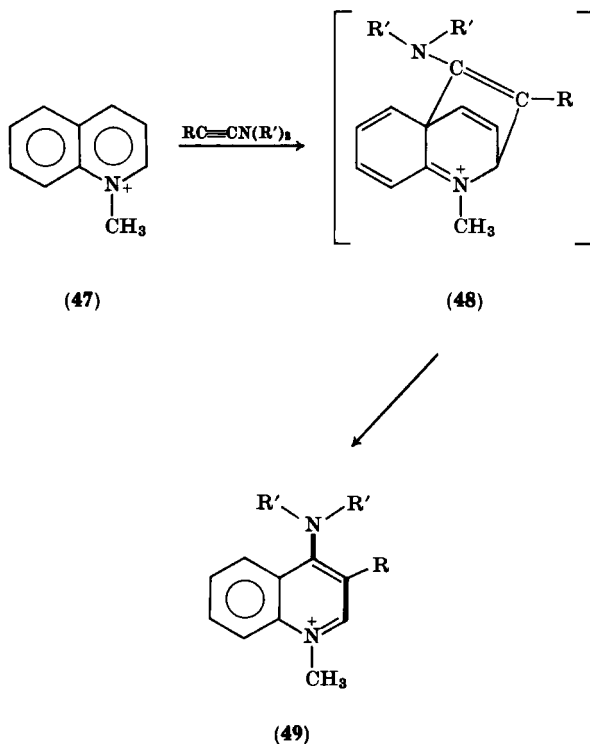
When simple isoquinolinium salts without substituents in the 3-position are used, the adducts (e.g., **46**) are more reactive to nucleophiles than is the starting material and, almost without exception, undergo attack by another mole of the alkene.⁹ In the light of these observations it would be desirable to have a reexamination of the products obtained by Fuks *et al.*²⁷ (by addition of ynamines to isoquinolinium salts) to make certain that the initial addition is really $2 + 2$ and not $4 + 2$.

C. OTHER AROMATIC QUATERNARY SALTS

The only example found of an aromatic quaternary salt undergoing $4 + 2$ cycloaddition, outside those discussed in Sections A and B above, is the reaction of 1-methylquinolinium iodide (**47**) with ynamines to afford 1-methyl-3-substituted-4-dialkylaminoquinolinium salts (**49**), presumably via loss of a C_2 unit from the cycloadduct (**48**).²⁷ A systematic search of aromatic quaternary salts using strongly nucleophilic addends will likely afford additional examples of this type of cyclization.

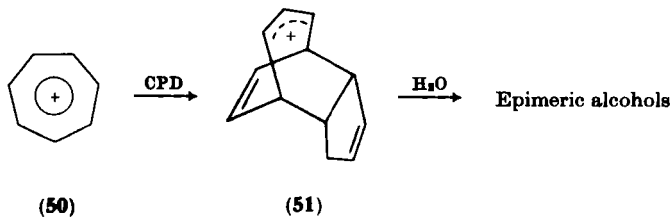
²⁸ C. K. Bradsher and F. H. Day, *Tetrahedron Lett.*, 409 (1971).

²⁹ C. K. Bradsher, F. H. Day, A. T. McPhail, and P. Wong, *Tetrahedron Lett.*, 4205 (1971).



D. CATIONIC AROMATIC SYSTEMS CONTAINING NO NITROGEN

In the presence of water the tropylium ion (50) has been found to undergo polar cycloaddition of the 4 + 2 type. Ito and Itoh³⁰ found that cyclopentadiene reacted with the tropylium ion to afford a 90% yield of a complex mixture of alcohols, all of which could be derived from the allylic cation (51).



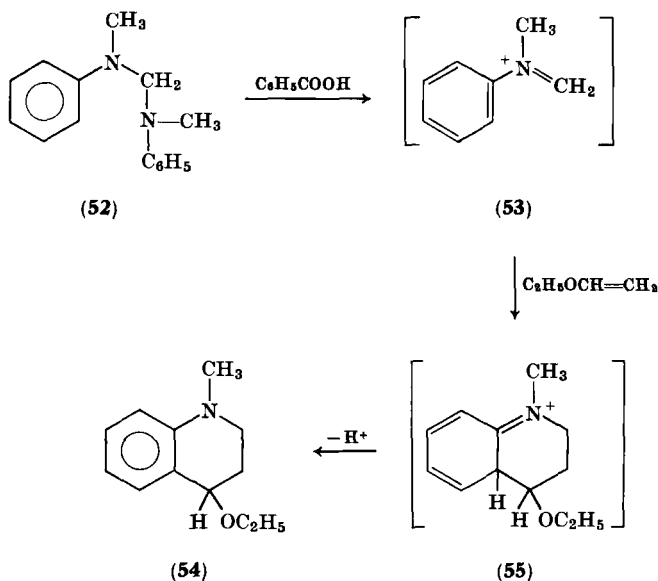
³⁰ S. Ito and I. Itoh, *Tetrahedron Lett.*, 2969 (1971).

III. Polar Cycloadditions in Which the Electrophilic System Contains Two Atoms of an Aromatic Ring

A. ARYLIMINIUM SALTS

1. *N*-Alkyl Aryliminium Salts

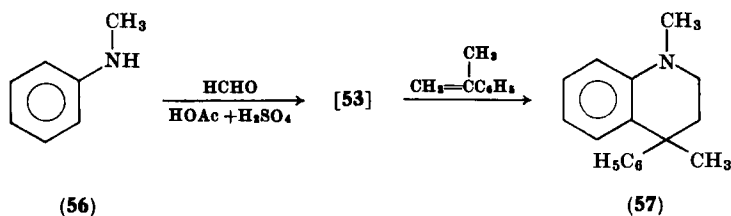
Swan³¹ has shown that *N,N'*-dimethyl-*N,N'*-diphenyldiamino-methane (52) in the presence of a catalytic quantity of benzoic acid



reacts with ethyl vinyl ether to afford 1-methyl-4-ethoxy-1,2,3,4-tetrahydroquinoline (54) in high yield. The reaction is believed to involve a 1,4-polar cycloaddition of an iminium salt (53) with ethyl vinyl ether followed by the loss of a proton from the initial adduct (55). The same iminium salt (53) is a likely intermediate in the reaction by which *N*-methylaniline (56) reacts in acidic medium with formaldehyde and α -methylstyrene to afford a 67% yield of 1-methyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (57).³²

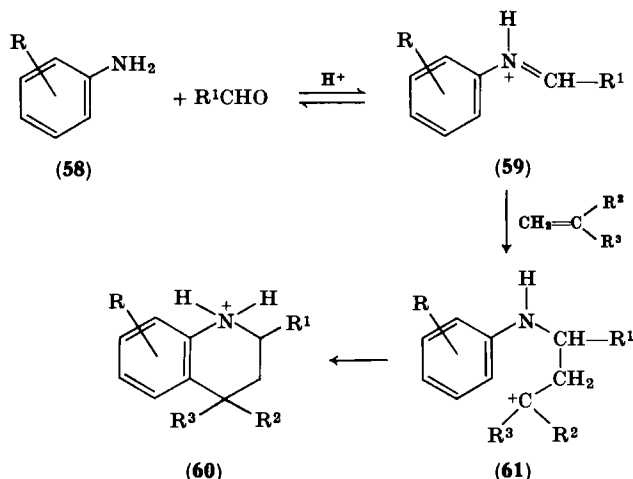
³¹ G. A. Swan, *Chem. Commun.*, 20 (1969).

³² K. D. Hesse, *Ann. Chem.* **741**, 117 (1970).



2. N-Protonated Aryliminium Salts

Hesse³² has made a much more extensive study of the reaction of aryl primary amines (58) with higher aldehydes (see 59) and a suitable alkene, usually styrene or α -methylstyrene, and found that high yields of tetrahydroisoquinoline (60) could be obtained even when an electron-withdrawing group was present in the aryl ring. Carbonium ion (61) appeared likely as an intermediate.



3. Lewis Salts of Arylimines

Povarov³³⁻³⁷ showed that Schiff bases, normally inert toward alkenes, react with boron trifluoride to form salts (62) which react readily and

³³ L. S. Povarov and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 955 (1963).

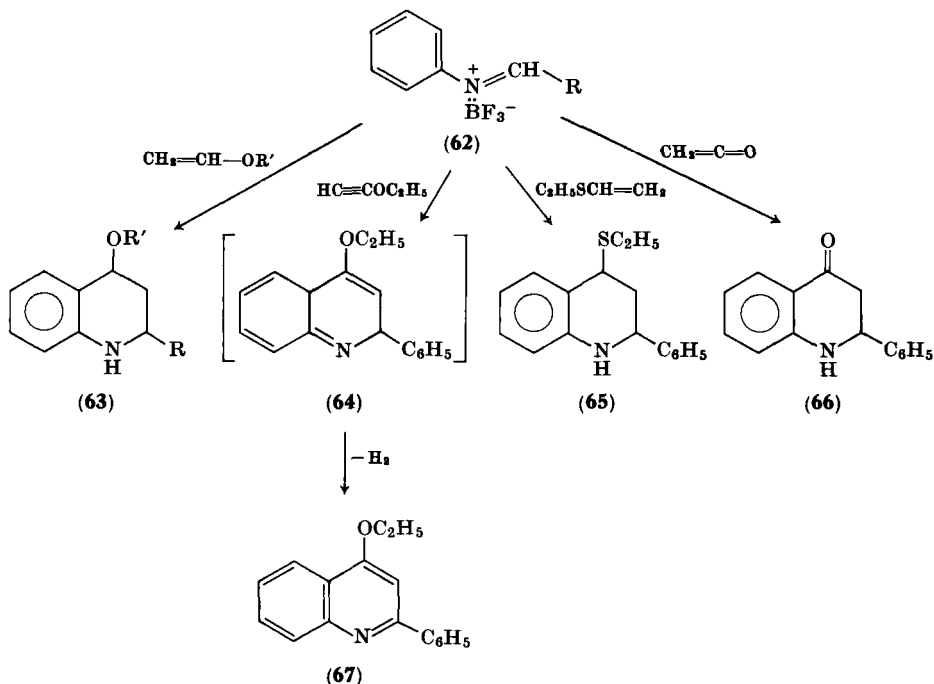
³⁴ L. S. Povarov, V. K. Grigos, and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2039 (1963).

³⁵ L. S. Povarov, V. I. Grigos, R. A. Karakhanov, and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 179 (1964).

³⁶ L. S. Povarov, V. I. Grigos, R. A. Karakhanov, and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 365 (1965).

³⁷ L. S. Povarov, *Russ. Chem. Rev.* **36**, 656 (1967).

regiospecifically with a variety of substrates (Scheme 1). Ethyl vinyl ether and ethyl vinyl sulfide react in analogous fashion to yield tetrahydroquinoline derivatives (**63** and **65**). Ethoxyacetylene does not yield



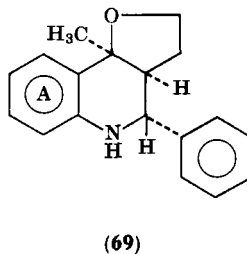
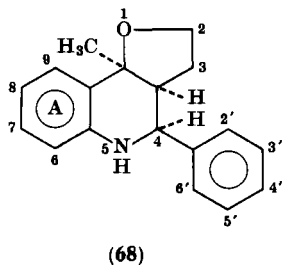
SCHEME 1. Cycloaddition of BF_3 Salts of Schiff Bases

the expected dihydroquinoline (**64**) but instead the fully aromatized derivative **67**. Of this group, ketene proved the poorest nucleophile, affording only a 25% yield of the 2,3-dihydroquinolone (**66**). Vinyl ethers as a class appeared to be superior nucleophiles, and of these, dihydrosylvan (2-methyl-4,5-dihydrofuran) appeared most reactive.^{35, 38} Elslager and Worth³⁹ have reinvestigated this cycloaddition using the boron trifluoride salt from benzylidene aniline (**62**, $\text{R} = \text{C}_6\text{H}_5$) and shown that the product is not homogeneous as originally claimed,³⁵ but consists of a mixture of the two stereoisomers **68** and **69** in approximately equal parts. Since these products possessed antimalarial activity, a

³⁸ B. M. Mikhailov, L. S. Povarov, G. I. Grigos, and R. A. Karakhanov, *Izv. Akad. Nauk., SSSR, Otd. Khim. Nauk*, 1693 (1964).

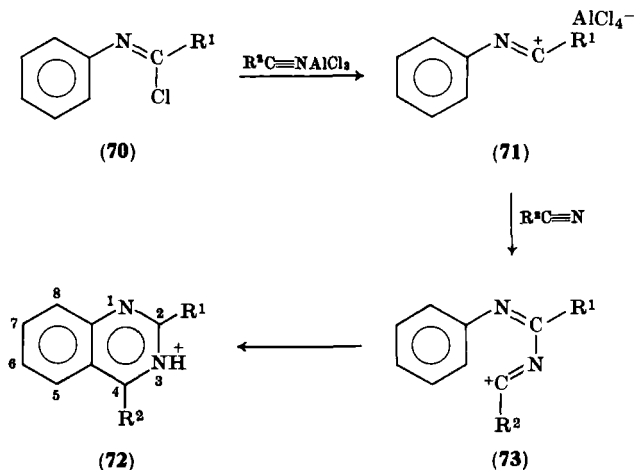
³⁹ E. F. Elslager and D. F. Worth, *J. Heterocyc. Chem.* **7**, 538 (1970).

large number of analogs were synthesized^{40, 41} with additional rings fused on ring A, the usual substituent in the phenyl group being 4'-methoxyl or hydroxyl.



B. NITRILIUM SALTS

Perhaps the earliest examples of a polar cycloaddition are some involving nitrilium salts. Meerwein *et al.*⁴² found that *N'*-arylacylimido chlorides (70) in the presence of Lewis acids (usually added in the form



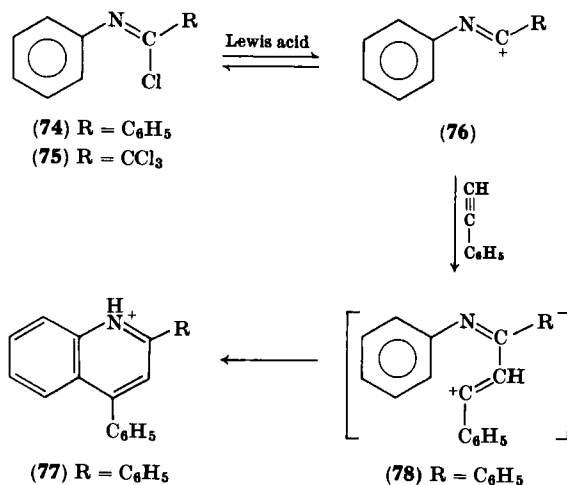
⁴⁰ S. C. Perricone, D. F. Worth, and E. F. Elslager, *J. Heterocycl. Chem.* **7**, 538 (1970).

⁴¹ D. F. Worth, S. C. Perricone, and E. F. Elslager, *J. Heterocycl. Chem.* **7**, 1353 (1970).

⁴² H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig, *Chem. Ber.* **89**, 224 (1956).

of a complex with a suitable nitrile) reacted with the nitrile to afford a 2-phenyl 4-substituted quinazolinium salt (72). The reaction was believed to occur stepwise, with the nitrilium ion (71) which was first formed reacting with the nitrile to produce a second nitrilium ion (73) which cyclized by electrophilic attack on the anilino rings. Of the large number of examples given R^1 was limited to phenyl, trichloromethyl, or dichloromethyl, while R^2 varied over a large range. Except in a few cases in which R^2 was electron-attracting, yields over 50% were realized. Of interest from the mechanistic standpoint was the observation that when methyl groups were introduced into both the ortho positions of the *N*-aryl group blocking cyclization, it was possible to isolate the dimethyl derivative of the nitrilium salt (73).

The same general method was used by Schmidt⁴³ (see 74) to generate nitrilium ions for addition to phenylacetylene. Normal addition of the nitrilium ion (76) occurred, affording the hydrobromide (77) of 2,4-diphenylquinoline, presumably via the carbonium ion (78). Interestingly, the analogous *N*-arylacylimido chloride in which the *R* group was

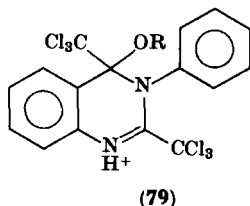


CCl_3 (75) was found not to attack the triple bond of phenylacetylene, but to react preferentially with the $C=N$ bond of another molecule of starting material (75), yielding 79.⁴

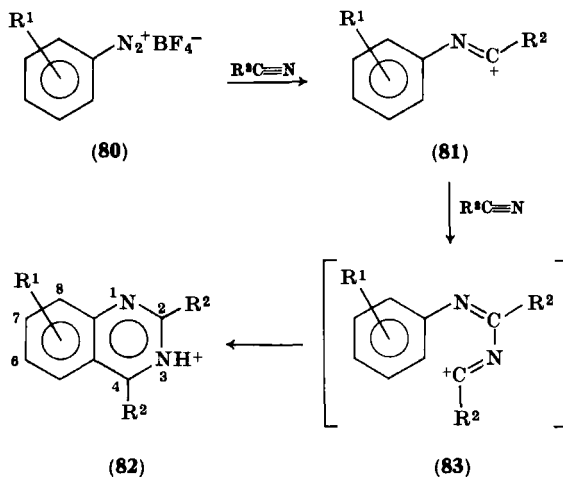
An alternative method of generating nitrilium salts for a cycloaddition reaction is by the decomposition of an aryldiazonium fluoroborate (80) in the presence of a suitable nitrile. This method has the disadvantage

⁴³ R. R. Schmidt, *Angew Chem., Int. Ed. Engl.* **3**, 804 (1964).

that the nitrilium ion (**81**) first formed reacts immediately with unreacted nitrile to form a second nitrilium ion (**83**). This cyclizes to a disubstituted



quinazoline salt (**82**) which inevitably has like substituents at positions 2 and 4. With benzonitrile the yields for several substituted diazonium salts (**80**, $R^1 = \text{CH}_3, \text{Cl}$) were in the range of 22–78%. Newer methods now available for the syntheses of nitrilium salts⁴⁴ should open the way to their wider application in cycloaddition.



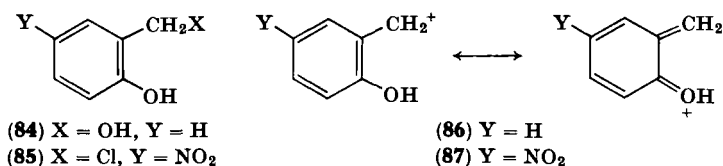
C. THE *o*-HYDROXYBENZYL CATION AND ITS CONGENERS

A simple alkenophile is the *o*-hydroxybenzyl cation (**86**), which may be generated either by the action of acid on *o*-hydroxybenzyl alcohol (**84**) or of a Lewis acid (e.g., SnCl_4) on an *o*-hydroxybenzyl chloride (e.g., **85**). The cation is unstable and is usually generated in the presence of the alkene to which it is to be added. Wakselman and Vilkas⁴⁵ showed that

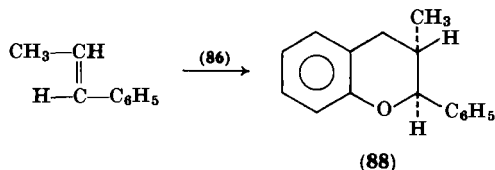
⁴⁴ R. F. Borch, *J. Org. Chem.* **34**, 627 (1969).

⁴⁵ M. Wakselman and M. Vilkas, *C.R. Acad. Sci.* **258**, 1526 (1964).

the cation generated from the alcohol **84** added (25–64% yield) to alkenes having an aryl group. Schmidt⁴⁶ showed that the cycloaddition of

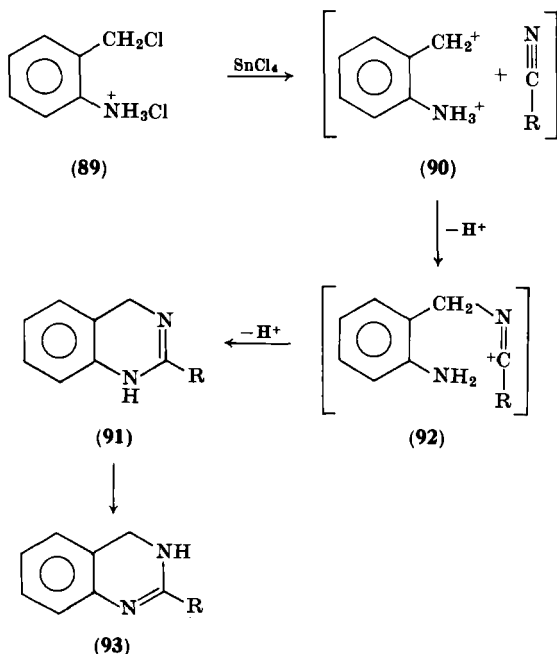


86 with *trans*- β -methylstyrene to form the chromane (**88**) occurred regio- and stereospecifically. He also showed that the nitro cation (**87**)



underwent cycloaddition in good yield even with relatively unreactive alkenes such as cyclohexene (82%) and 2-pentene (88%).

The *o*-aminobenzyl cation, as its hydrochloride (**90**), may be an intermediate in the reaction of 2-chloromethylaniline hydrochloride (**89**)



⁴⁶ R. R. Schmidt, *Tetrahedron Lett.*, 5279 (1969).

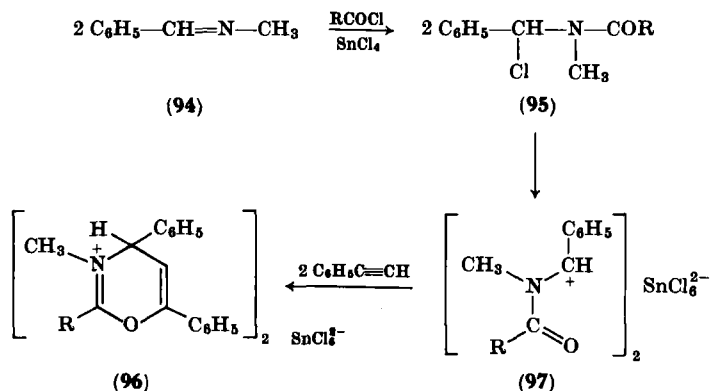
with nitriles in the presence of stannic chloride to yield dihydroquinazoline (93).⁴⁷ To assume that any part of this transformation is a cycloaddition might appear arbitrary, but if the formation of the nitrilium ion (92) involves simultaneous deprotonation of the amine salt, the cyclization (see 91) would at least be parallel to the formation of chromanes from the *o*-hydroxybenzyl cation (86), a reaction which does occur without violation of the cis rule. In any case, this synthesis of 3,4-dihydroquinazoline is a convenient one and with a wide variety of aliphatic and aromatic nitriles, yields of 68–100% may be expected.

IV. Polar Cycloadditions Involving Open-Chain Electrophilic Systems

A. *N*-METHYLENIUM AMIDE SYSTEMS

1. *N*-Methyl-*N*-Methylenium Amides

In 1965 Schmidt⁴⁸ showed that a mixture of *N*-methylbenzylideneimine (94), an acid chloride, and phenylacetylene would react in the

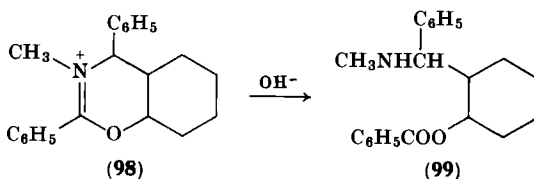


presence of stannic chloride to yield *N*-methyl-4*H*-1,3-oxazinium salts (96). There is good evidence that there is an initial attack of the acid chloride on the Schiff base (94), forming an *N*-methyl-*N*- α -chlorobenzylamide (95). Loss of a chloride ion from the amide (95) would yield an *N*-methyl-*N*-methylenium amide ion (97) which undergoes 1,4-cycloaddition with phenylacetylene. Yields were only fair with substituted benzoyl halides (37–41%) but acetyl chloride gave a 92% yield

⁴⁷ M. Lora-Tomayo, R. Madronero, and C. Garcia-Muñoz, *Chem. Ber.* **94**, 208 (1961).

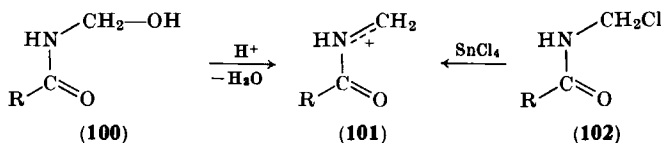
⁴⁸ R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.* **4**, 241 (1965).

of the expected oxazinium salt (**96**, R = Me). More recently it was shown⁴⁹ that the same three-component mixture technique could be applied to the formation of a dihydro-1,3-oxazine (**98**) from cyclohexene, the product being isolated in 50% yield as the ring-opened basic ester (**99**).



2. Simple N-Methylenium Amides

After the acridizinium system (Section II, A), the most-studied electrophile in polar cycloaddition is the *N*-methylenium amide system (**101**).



The reactive cation (**101**) may be generated either by protonation and dehydration of the *N*-hydroxymethylamide (**100**)⁵⁰ or by the Lewis acid-catalyzed removal of a chloride ion from an *N*-chloromethylamide (**102**).⁵¹ Addition of the cation (**101**) to benzonitrile afforded a 2,6-diphenyl-4*H*-1,3-oxadiazinium salt (**103**) in 39% yield, while addition to phenylacetylene gave 2,6-diphenyl-4*H*-1,3-oxazinium hexachlorostannate (**104**) in 99% yield.⁵¹

The addition of alkenes to *N*-methylenium amide cations is stereospecific⁵² in the sense that it obeys the "cis principle" of Alder and Stein,⁵³ *cis*-2-butene giving a *cis* product (**105**, R = R¹ = Me) and the *trans* isomer giving *trans* product (**105**, R = R³ = Me).⁵² The cycloaddition of unsymmetrical alkenes is highly regiospecific.^{50, 52} Knowing how the alkene will react with a large cation allows prediction of the product (**105**). Thus styrene, butadiene, and vinyl acetate all react so that its substituent appears at position 6 of the dihydrooxazinium salt (**105**, R = Ph, vinyl, or OAc).

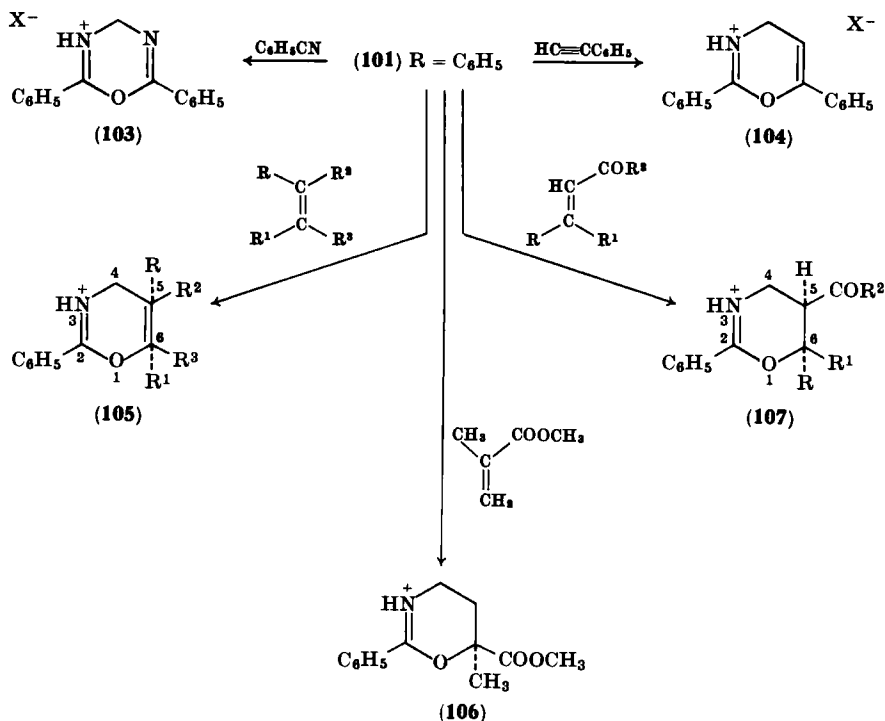
The *N*-methylenium benzamide cation (**101**, R = Ph) is sufficiently electrophilic to react with even electron-deficient alkenes⁴⁹ such as

⁴⁹ R. R. Schmidt, *Chem. Ber.* **103**, 3242 (1970).

⁵⁰ W. Seeliger and W. Diepers, *Ann. Chem.* **697**, 171 (1966).

⁵¹ R. R. Schmidt, *Chem. Ber.* **98**, 344 (1965).

⁵² R. R. Schmidt, *Angew. Chem.* **81**, 576 (1969).

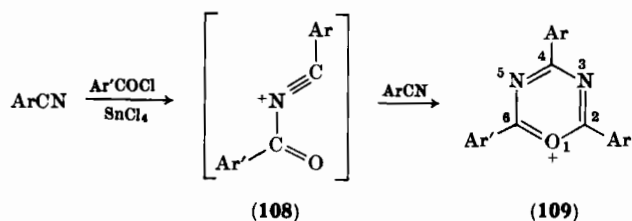


α,β -unsaturated ketones. All the unsaturated ketones studied had one or more substituents at the β -position and all reacted to give the expected orientation with the carbonyl group at position 5 (107). The addition of methyl methacrylate occurred with the methyl and carbomethoxy appearing exclusively at position 6 (106). Schmidt⁴⁹ regarded this orientation as contrary to the rules of electrophilic 1,2-addition and characterized it as a further indication of the concerted nature of the cycloaddition.

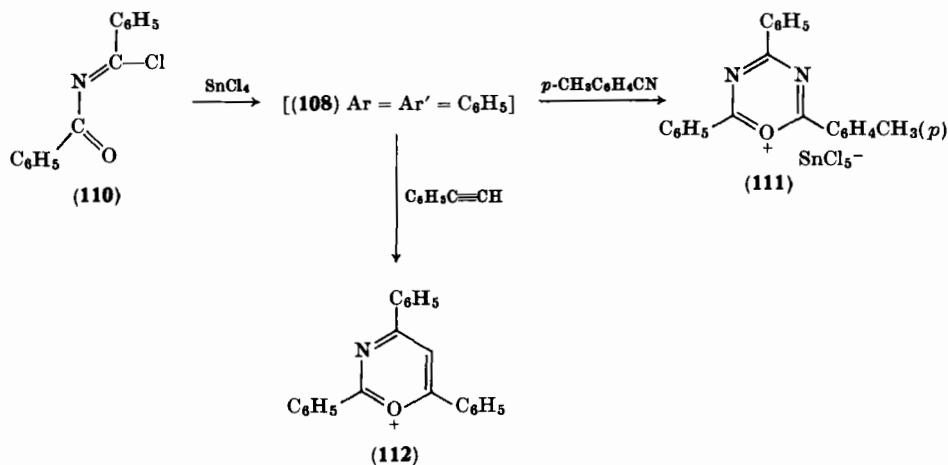
B. *N*-AROYLNITRILIUM SALTS

Schmidt⁵¹ showed that reaction of 1 mole of aroyl chloride with 2 moles of an aryl nitrile in the presence of stannic or zinc chloride afforded in excellent yields a 2,4,6-triaryldiazapyrylium salt (109) in which at least two of the aryl groups (at positions 2 and 4) were alike. It was presumed that the intermediate was an aroylnitrilium ion (108).

Evidence was provided for such an interpretation of the reaction by showing that *N*-benzoylbenzimidoyl chloride (110) with *p*-tolunitrile reacted in the presence of stannic chloride to afford a 56% yield of the

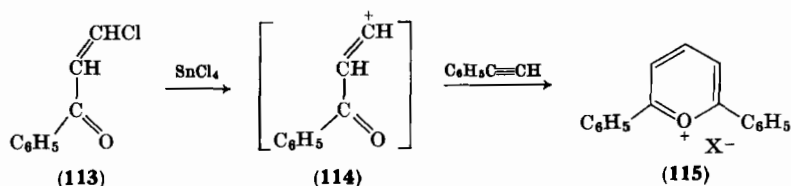


2-*p*-tolyl-4,6-diphenyl-3,5-diazapyrylium salt (111). Schmidt⁵¹ also showed that the benzimidoyl chloride (110) similarly reacted with phenylacetylene in the presence of stannic chloride, affording a triphenyl-3-azapyrylium salt (112) in 64% yield.

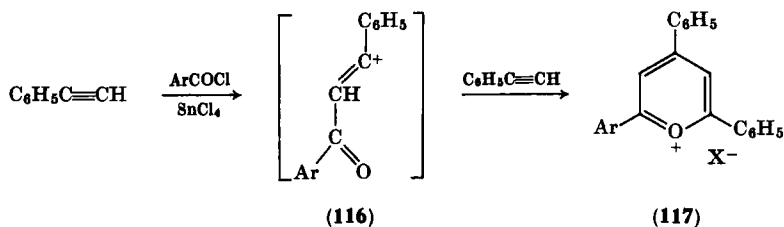


C. β -ACYLVINYL CARBONIUM IONS

Schmidt⁵¹ demonstrated that a carbon chain analog of the 110–112 transformation exists. He found that β -chlorovinyl phenyl ketone (113) reacts in the presence of stannic chloride with phenylacetylene to afford a small yield of 2,6-diphenylpyrylium salt (115), presumably via the



benzoylvinyl carbonium ion (114). A more useful application of the same type of cycloaddition involves the creation of the intermediate carbonium ion (116) via acylation of phenylacetylene, followed by cycloaddition with a second mole of phenylacetylene to give 2-aryl-4,6-diphenylpyrylium salts (117) in 55–81% yields.⁵⁴



V. The Mechanism of Polar Cycloaddition

A. ALTERNATIVE MECHANISMS

Essentially two mechanisms have been offered for polar cycloaddition. The first of these is a nonsynchronous or two-step mechanism which involves attack of the electrophilic cation on the nucleophile to produce a new cation, which undergoes cyclization by attack on suitably located π -electrons or an unshared electron pair. This mechanism has been advocated at some time by seemingly all the major workers in the area with the exception of Fields *et al.*⁶ The alternative view, now held by Schmidt,^{49, 52, 56} is that the reaction is synchronous. In this section, an effort will be made to reconcile each of the two theories to some observations which have been made concerning polar cycloaddition.

B. EXPERIMENTAL EVIDENCE

1. Regiospecificity of Cycloaddition

Huisgen *et al.*⁵⁸ have pointed out that in the Diels–Alder reaction “the electronic character of the substituents has practically no influence on the direction of addition.” The same point of view has been taken by Fields *et al.*⁶ and by Schmidt⁴⁹ to explain certain apparent anomalies

⁵³ K. Alder and G. Stein, *Angew. Chem.* **50**, 510 (1937).

⁵⁴ R. Schmidt, *Angew. Chem., Int. Ed., Engl.* **3**, 387 (1964).

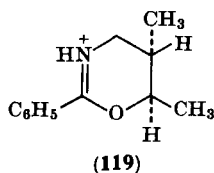
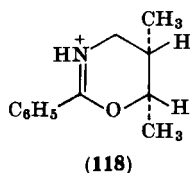
⁵⁵ R. R. Schmidt and R. Machat, *Angew. Chem., Int. Ed. Engl.* **9**, 311 (1970).

⁵⁶ R. Huisgen, R. Grashey, and J. Sauer, “The Chemistry of Alkenes” (S. Patai, ed.) Vol. I, p. 914. Wiley (Interscience), New York, 1964.

in the orientation of polar cycloaddition. Without exception (see V, B, 4) the direction of polar cycloaddition is the one which would be predicted if the first step was the addition of a large cation to the nucleophile.

2. Conformity with the Cis-Principle

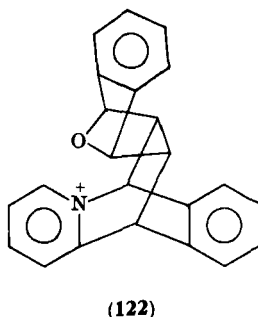
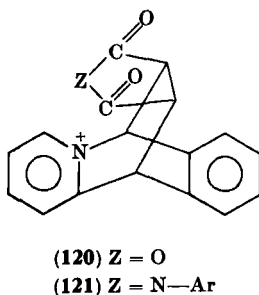
The demonstration⁵² that the polar cycloaddition of *cis*-butene and *trans*-butene gave adducts **118** and **119** in which the stereochemistry was preserved, satisfied an important requirement for synchronous cycloaddition. While the conformity to the cis principle does not exclude the



possibility of a two-step reaction, it does mean that if such a mechanism is operative, the interval between the first and second steps must be shorter than that required for rotation about a carbon-carbon bond.

3. Stereospecificity of Cycloaddition Not Covered by the Endo-Addition Rule⁵⁷

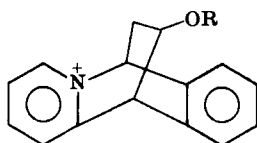
In cycloaddition reactions involving the acridizinium and isoquinolinium ions, the presence of a positive charge leads with great stereoselectivity to products which could not be predicted by the rule of Alder and Stein.⁵³ A charge-transfer complex arising from the attraction



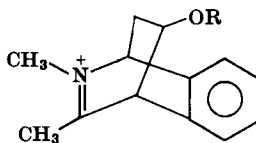
between the positive charge of the nitrogen atom and the unshared electrons of the ring heteroatom is the probable cause of the anti (with regard to the benzene ring) orientation of **120**,⁷ **121**,¹⁰ and **122**.¹⁴ Another

⁵⁷ See Schmidt,⁵⁴ p. 910.

type of polar effect leads to the stereospecific addition of vinyl ethers. The orientation of the alkoxyl group syn (to the phenylene ring) in adducts **123** and **124**, obtained from the acridizinium and isoquino-

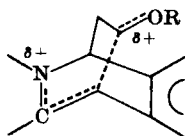


(123)

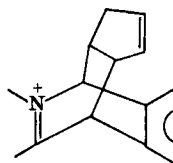


(124)

linium salts, probably arises from repulsions in the transition state (**125**) of the second step. Evidence is available¹³ that cyclopentadiene likewise



(125)



(126)

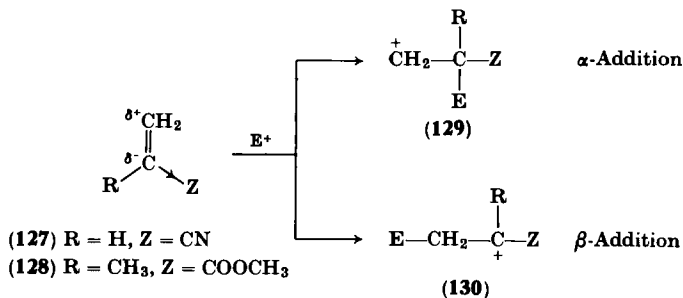
adds stereospecifically to the isoquinolinium and acridizinium systems. The orientation in both cases (**126**) is again that which would give maximum separation of like charges in the transition state. Day⁹ has used the same charge-separation argument as the rationale for the predominantly (20 : 1) endo character of the addition of cyclopentadiene to the tropylium ion (**50**).

4. Failure of Acrylonitrile and Methyl Methacrylate to Undergo Polar Cycloaddition with the Predicted Orientation

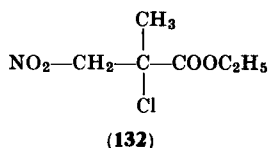
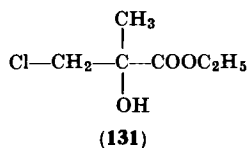
Fields *et al.*⁶ and Schmidt⁴⁹ made closely parallel observations concerning polar cycloaddition of ethylenes substituted at the α -position by an electron-withdrawing group and having no substituent at the β -position. In both cases the product observed was that to be expected if the electrophile had added to the β -carbon atom. Since it is clear that the normal ground-state polarization of acrylonitrile (**127**) and methyl methacrylate (**128**) should tend to destabilize the cation produced by β -addition, it was concluded that the orientation of polar cycloadditions could not be predicted by the rules of electrophilic addition and that this apparent anomaly pointed toward a more concerted type of cycloaddition reaction.

All the numerous other polar cycloaddition reactions studied show a regiospecificity explicable only on polar grounds and thus warrant examination of how acrylonitrile (**127**) and methyl methacrylate (**128**)

actually react with polar reagents. These ethylenes, unsubstituted at one end and having an electron-withdrawing group at the other, almost uniformly react with unsymmetrical polar reagents (other than hydrogen



halides) in an orientation which would be produced if the more positive end of the polar reagent had attacked the unsubstituted end of the double bond. With almost the same uniformity, the observed orientation has been offered as the primary evidence that the addition in question has occurred by a radical mechanism.^{58, 59} Among the few unsymmetrical reagents which have been described⁶⁰ as adding by an electrophilic mechanism is hypochlorous acid. If hypochlorous acid is added to ethyl methacrylate, the chief product (other than ethyl 2,3-dichloro-2-methylpropanoate) is ethyl 3-chloro-2-hydroxy-2-methylpropanoate (**131**),⁶¹ explicable if the initial attack of the positive chlorine had been at the β -carbon atom of the double bond. Nitrosyl chloride, which is also



believed⁶² to add electrophilically, adds to ethyl methacrylate to yield (in addition to ethyl 2,3-dichloro-2-methylpropanoate) ethyl 3-nitro-2-chloro-2-methylpropanoate (**132**). The formation of **132** can be explained by assuming an attack at the β -carbon atom by the nitrosonium

⁵⁸ E.g., C. F. Koelsch and V. Boekelheide, *J. Amer. Chem. Soc.* **66**, 412 (1944).

⁵⁹ E.g., H. Schechter, F. Conrad, A. Daulton, and R. B. Kaplan, *J. Amer. Chem. Soc.* **74**, 3052 (1952).

⁶⁰ J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," p. 612. McGraw-Hill, New York, 1968.

⁶¹ G. F. Bloomfield, E. H. Farne, and C. G. B. Hose, *J. Chem. Soc.*, 800 (1933).

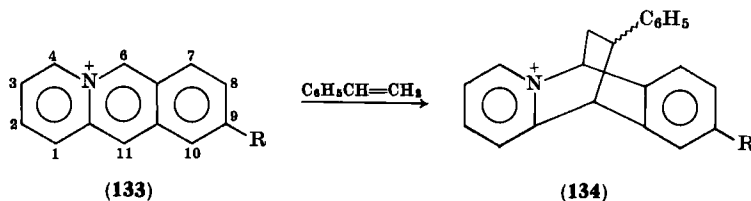
⁶² See Koelsch and Boekelheide,⁵⁸ p. 613.

ion (either as such or as the positive end of the dipole) followed by reaction of the chloride ion at the α -position with subsequent oxidation of the nitroso group.

These "anomalous" reactions can be rationalized by assuming that the difference in the energy involved between the formation of a primary carbonium ion as in **129** and of a secondary (or tertiary) carbonium ion destabilized by an electron-withdrawing group (as in **130**) must be close enough to permit steric influences to be dominant. Whereas the small proton can easily bring about α -addition (**129**),^{63, 64} a much larger electrophile usually favors β -addition (**130**). The implications of this theory are far-reaching and outside the limits of this review.

5. *Dependence of the Rate of Addition of Styrene to Acridizinium Nucleus upon Electron Deficiency at Position 6*

The rate of cycloaddition (see **134**) of styrene with the acridizinium nucleus (**133**) varied directly with the electron-withdrawing capacity of a



substituent at position 9. The observed rates lead to a significant Hammett plot (Fig. 1) when para σ -values were used. These experiments show that the positive charge at position 6 is the cause of, and not simply incidental to, the cycloaddition.

6. *Failure of Norbornene to Give Rearranged Products*

In spite of the known tendency of norbornene and related systems to undergo rearrangements of the Wagner–Meerwein type during electrophilic addition,⁶⁵ no such rearrangement was observed when norbornene underwent cycloaddition with the acridizinium¹⁴ or the *N*-methylenium benzamide cation.⁴⁹ As Schmidt⁴⁹ correctly pointed out, this lack of rearrangement is an argument for a concerted reaction. Alternatively, if the cycloaddition is nonsynchronous, the time interval between step 1 and step 2 must be very short.

⁶³ J. G. Erickson, U.S. Patent 2,524,011 (1950); *Chem. Abstr.* **45**, 2016 (1951).

⁶⁴ P. L. Pickard and H. L. Lochte, *J. Amer. Chem. Soc.* **69**, 14 (1947).

⁶⁵ P. D. Bartlett, in "Organic Chemistry" (H. Gilman, ed.), Vol. III, pp. 55–70. Wiley, New York, 1953.

7. *Change in the Rate of Cycloaddition Produced by Substitution at the Meso Positions of the Acridizinium Ion*

The introduction of methyl groups into the two meso (9 and 10) positions of anthracene affords a "diene" significantly more reactive

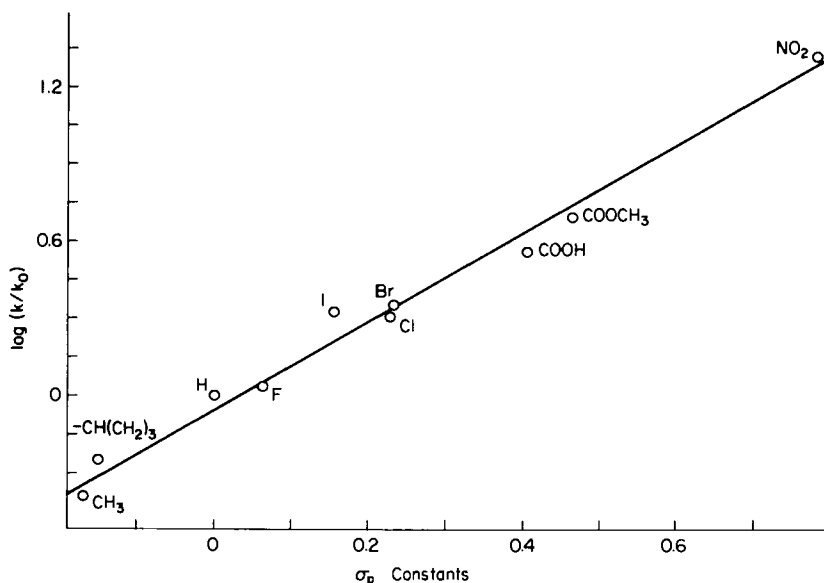
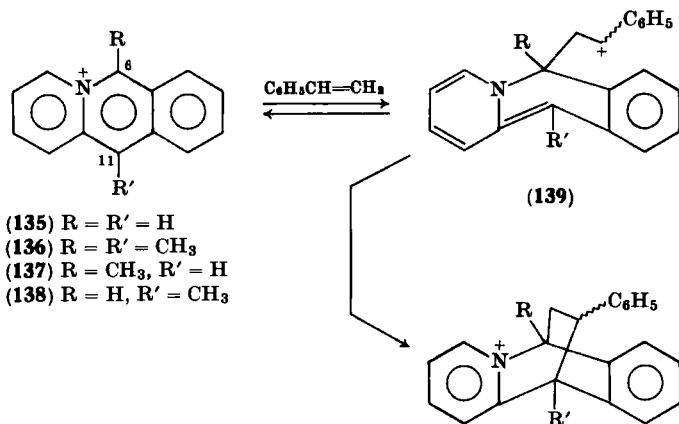


FIG. 1. Plot of $\log k/k^0$ vs. σ -constants for reaction of styrene with the acridizinium ion. See Westerman and Bradsher;¹⁶ by permission of American Chemical Society.

toward maleic anhydride than is the parent compound.⁶⁶ The result is easily explicable in terms of the electron release of methyl groups. One would predict that the same type of electron release, combined with steric factors, would make the addition of styrene to 6,11-dimethyl-acridizinium ion (**136**) *slower* than to the acridizinium ion (**137**), since these cations show inverse electron demand. Actually the dimethyl acridizinium (**136**) reacts approximately eight times as fast as the parent compound (**135**). A clue to the understanding of this apparent anomaly is provided by the rates of cyclization of *meso*-monomethylacridizinium cations (**137** and **138**). If the methyl group is introduced only into position 6 (see **137**) adjacent to the quaternary nitrogen, the rate of cyclization is roughly halved, showing a decreased rate, as expected. If the methyl group is introduced instead at the other meso position, position 11 (see **138**), one finds an enhancement in the rate of cycloaddition of about

⁶⁶ W. E. Bachmann and M. C. Kloetzel, *J. Amer. Chem. Soc.* **60**, 481 (1938).

15 times that of the parent compound. All of these observations can be reconciled by the assumption of a two-step reaction, the first step of which is reversible. The concentration of the intermediate carbonium ion (139) is, for both steric and electronic reasons, adversely affected by substitution at position 6. If the final step of the cyclization is considered as

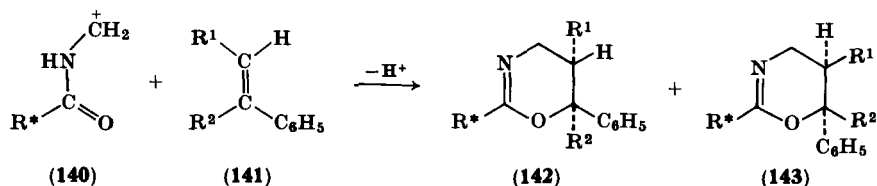


involving intramolecular attack of a benzyl carbonium ion upon an enamine (139), the introduction of an electron-releasing methyl group at position 11 would understandably make that enamine more vulnerable to attack. The opposite effects on reaction rate produced by methyl substitution at the two reactive sites for cycloaddition are convincing evidence that in polar cycloaddition the two new σ -bonds are formed by different processes.

8. Evidence Concerning the Nature of the Transition State Derived from Cycloaddition of a Chiral N-Methylenium Amide

Schmidt and Machat⁵⁵ attempted to learn something concerning the geometry of the transition state for polar cycloaddition by carrying out cycloaddition reactions using optically active α -methoxy- α -phenyl-N-methylenium acetamide ion (140, $\text{R}^* = \text{PhCHOCH}_3$). The results in Table III show that the ratio of diastereoisomers obtained is little affected by the presence or nature of substituents at the β -position of styrene (141, $\text{R}^1 = \text{H}$ or alkyl) but is significantly changed when a methyl group is introduced at the α -position. From this, Schmidt concluded (probably correctly) that in the transition state the group R^2 is very much nearer to the chiral group than is R^1 . It is more difficult to agree with his conclusion that, "This finding is only consistent with the

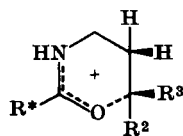
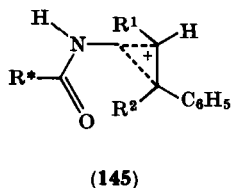
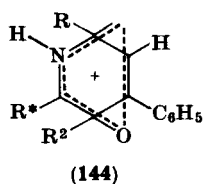
TABLE III

ADDITION OF OLEFINS TO CHIRAL *N*-METHYLENIUM AMIDES^a

R ¹	R ²	Ratio yield 142/143
H	H	1.8
Me	H	1.8
Et	H	1.8
<i>n</i> -Pr	H	1.7
H	Me	1.1

^a See Schmidt and Machat,⁵⁵ by permission of Verlag Chemie.

transition state [144] previously discussed for synchronous cyclo-additions."

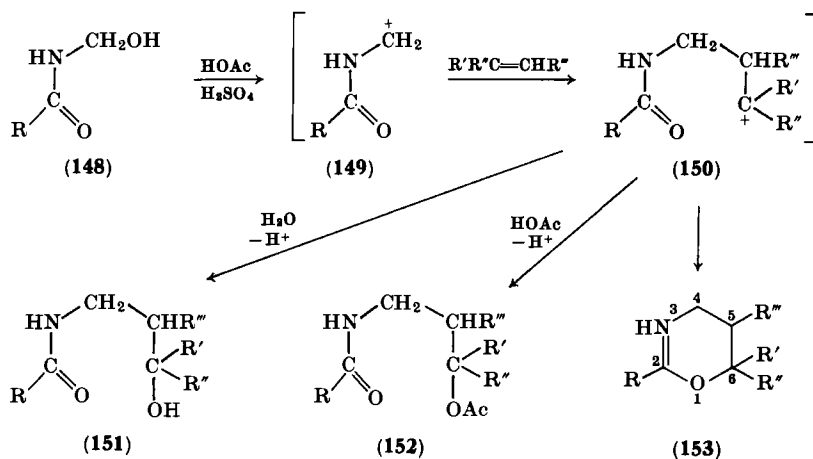
(146) R² = C₆H₅, R³ = CH₃(147) R² = CH₃, R³ = C₆H₅

It was also pointed out that the results were not consistent with the typical transition state (145) for a primary electrophilic attack on an olefin.

If, on the other hand, it is assumed that the initial electrophilic attack is reversible and that addition can occur above or below the plane defined by the alkenes, two diastereomeric cations would be formed, perhaps in approximately equal concentration. Due to the proximity of the chiral acyl group, the probability of achieving the transition states (approximately represented by 146 and 147) would be unequal and a function of the difference in sizes of groups R² and R³ (146 and 147).

9. The Hydroxyl Derivatives Obtained by Seeliger and Diepers

Seeliger and Diepers⁵⁰ carried out their study of the cycloaddition reactions of the *N*-methylenium amide ion (149) by generation of the ion through the action of sulfuric acid on an acetic acid solution containing an *N*-hydroxymethyl amide (148) in the presence of a suitable alkene. At least a third of the alkenes investigated yielded, in addition to the expected 5,6-dihydrooxazinium salts (153), hydroxy (151) and acetoxy (152) amides which contained the carbon chain of the alkene. Seeliger and Diepers explained the product distribution as being a



consequence of a competition reaction in which the cationic intermediate (150) formed by an initial electrophilic addition may either cyclize directly to the dihydrooxazinium (153) or attack a molecule of acetic acid affording the acetate (152) or a molecule of water (formed in the first step) to give the alcohol (151).

While these observations might appear to be convincing evidence for an electrophilic two-step mechanism, it must be pointed out that Seeliger and Diepers did not demonstrate that the 5,6-dihydrooxazinium salts, once formed, would not undergo ring-opening under the conditions of the reaction.

In summary, none of the observations made to date would be inconsistent with the concept of a concerted but nonsynchronous cycloaddition in which polar influences are of great importance in determining *regiospecificity* and in some cases *stereospecificity*.

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